ANNALS OF
INTERNAL MEDICINE

VOLUME 42 MARCH, 1955 NUMBER 3

ACUTE INFECTIOUS DISEASES IN PREGNANCY *

By CONRAD WESSELHOEFT, M.D., F.A.C.P., *Boston, Massachusetts*

THE subject of acute infectious diseases in pregnancy deals primarily with the effect of infections on the pregnant woman and her offspring. (1) The infection may pass off without injury and allow full term delivery of a normal child. (2) The infection may induce spontaneous abortion or premature labor on the part of the mother. Or (3) the infection may (a) cause the child to be born with a congenital form of the disease; (b) cause the death of the fetus in utero; or (c) bring about anomalies of fetal development resulting in minor or major congenital deformities.

We must not lose sight of the fact that pregnancy on the other hand may exert a profound influence on an existing infection. Pregnancy may convert a relatively quiescent localized pulmonary tuberculous lesion into a fulminating miliary type and shorten the life of the mother.[1] It is interesting that a tuberculous infection acquired during pregnancy is not nearly as serious for the mother as one acquired prior to conception.[1]

Influenced by this well known danger of pregnancy to the tuberculous patient, it is quite natural to attribute the severity of any infectious disease in the course of pregnancy to the pregnant state. Although we cannot deny that this may be so in individual cases, it is certainly not a general rule. With the increasing incidence of poliomyelitis in the child-bearing age, it has been easy to gain the impression on the hospital wards that pregnant women appeared to be unusually prone to extensive paralyses. Careful analysis of statistics shows that there is no evidence that the infection is more severe among pregnant women than among a comparable group of non-pregnant women.[2, 3] However, it has been shown that parturition in the acute phase of this disease increases the risk of extension of paralyses.[4]

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 6, 1954.

From the Haynes Memorial, Department of Infectious Diseases, Massachusetts Memorial Hospitals, Boston.

Aside from this question of case severity, there is evidence that the attack rate of poliomyelitis among pregnant women is higher than among an estimated control group of non-pregnant women. In other words, pregnancy increases susceptibility to poliomyelitis.[2, 4] If this is attributable to endocrine imbalance, it is worthy of note that some sufferers from bronchial asthma may experience complete freedom from asthmatic attacks during pregnancy even though they develop upper respiratory infections which ordinarily precipitate a bout of asthma.

Syphilis frequently results in premature labor with stillbirth usually after the fifth month, but the disease in the mother is not aggravated by the pregnant state. During pregnancy the spirochete of relapsing fever is said to give rise to the death of the fetus, and thereby abortion, in 92 per cent of the cases.[5]

Smallpox has the reputation of being unusually severe in pregnancy, when it is more apt to be confluent and hemorrhagic in type.[6, 7] Pregnancy is terminated in 30 to 69 per cent of the cases.[8] One of the reasons for the higher mortality of this disease in the course of pregnancy is the symbiosis of the beta hemolytic streptococcus in the pustular stage, which, in combination with abortion or stillbirth, leads to puerperal septicemia. Scarlet fever, on the other hand, is not unusually severe in pregnancy, and abortion is rare. Coccidioidomycosis [9] is apt to induce premature birth.

Typhoid fever and undulant fever are not unusually severe in pregnancy, but abortion may take place in prolonged high fever, though in all probability less frequently since the introduction of antiobiotic treatment.

Meningococcemia,[10] which today yields so promptly to the sulfonamides, no longer interrupts pregnancy. The latest evidence indicates that influenza A_1 in the early months of pregnancy does not appreciably add to the risk of stillbirth.[11] Measles, mumps, chickenpox, and rubella are not generally more severe in pregnancy. In these diseases, the incidence of abortion or premature birth is in ratio to the severity of the fever, although abortion can occur in mild cases. In rubella, the severity appears to bear no relation to the termination of pregnancy. Vaccinia, inoculated into five million inhabitants of New York City in 1947, was not aggravated by pregnancy, nor did it apparently influence the usual ratio of stillbirths.[12, 24] The common cold would appear to belong to this same benign category.

Congenital forms of infectious disease, such as syphilis, tuberculosis,[13] and toxoplasmosis,[13, 14] are quite different from congenital deformities resulting from maternal rubella. An infant may be born prematurely or at term with measles, chickenpox, mumps or rubella, and if so the disease is apt to be mild. This, however, is extremely rare, since the infant at term and for two months thereafter usually has a temporary congenital immunity which protects against these infections. Even before the days of gamma globulin it was not unusual for an infant under two months old to nurse from its mother who had measles without having the infant come down with

the disease.[6] The opposite is true with whooping cough which is so often fatal in the newborn.

It was not until 1941 when Gregg [15] discovered the relationship between congenital cataract and maternal rubella that the medical world became interested in the possible hidden dangers to the fetus of what one generally considers to be the minor diseases of childhood. Gregg's discovery was the result of his inquiry into the cause of congenital cataracts following in the wake of a particularly heavy epidemic of rubella in Australia the preceding year. (The term German measles is avoided because rubella is not a German form of measles or any other form of measles.) The Australian investigations also brought out the fact that rubella in the first four months of pregnancy was capable of inducing not only cataract but a pattern of damage during the embryologic formation of the eye, the ear and the heart. This triad, primarily of the lenticular, cochlear and cardiac primordia, gives rise singly or in combination to blindness, deafness, and patent ductus arteriosus. Babies with these congenital deformities are usually poor feeders, and sometimes hydrocephalic or microcephalic mental defectives. If they survive the first year, they are prone to develop dental malformations. All this has come to be known as the post-rubella syndrome.

The great bulk of evidence concerning the results of maternal rubella is based on the collecting of cases of congenital deformities which have been traced back to an attack of rubella in the mother during pregnancy. This method has brought out the fact that the danger lies in the first four months, and especially in the first twelve weeks or first trimester. Further analysis has indicated that blindness results from damage in the first six weeks of gestation, deafness and mongolism in the ninth week, patent ductus arteriosus in the first twelve weeks, and dental disturbance in the sixth to ninth week.[10, 16]

Swan [16] has collected a grand total of 939 cases of congenital deformities in children born of mothers who suffered an attack of rubella during pregnancy. In 870, or 92.7%, the mother had contracted the disease in the first four months.

I have collected reports [17b] of 180 normal babies born of mothers who had rubella during pregnancy, 70 of whom were from mothers who had rubella in the first three months.[18] * To this 70 I can now add 3 more of my own cases, one in the first month and 2 in the second month, giving a grand total of 73 normal babies born of mothers who were known to have rubella in the first trimester.

Collected reports [17b] from the literature comprise 31 miscarriages or stillbirths following rubella, 27 of which occurred in the first four months of pregnancy; to which 13 more can now be added from Ingalls et al.,[18] with 4 in the first trimester, giving a total of 44 miscarriages or stillbirths, 31 occurring in the first four months.

* Ingalls' [18] report included two series (Aycock and Ingalls, Fox and Bortin), which were part of my 1949 collection.

These three compilations of congenital deformities, normal births, and stillbirths must be considered separately. They have no direct relationship. They constitute variables from a mathematical point of view and cannot be utilized to give a constant ratio. Furthermore, these figures are derived from working backwards from the end result to the attack of rubella in pregnancy. Until a substantial series is collected by working from known cases of rubella to the end results, we are not justified in attempting to establish the mathematical risks of congenital deformities, miscarriages or stillbirths.

The only conclusions justified from these combined reports is that rubella in the course of pregnancy may give rise to congenital deformities in the infant; that the danger of this taking place lies in the first four months of pregnancy, especially in the first three months, and that the time of the attack governs the site of the primordial damage; that the fetus may be killed as a result of the infection; and, finally, that a normal full-term child may be born even though the mother contracted the disease in the first three months.

Various authors have attempted to determine the risk to the fetus. The first reports from Australia suggested that if a woman contracted rubella in the first two months of pregnancy the chances of her giving birth to a congenitally defective child were close to 100%. This idea has been radically changed. Swan [16] has ventured to suggest an 80% risk of deformities when the maternal attack is in the first four months, though he admits the method of collecting data favors the collection of deformities as against normal births. Collins [19] in a recent study in Australia offers a risk of 70 to 80% deformities in the first four months of pregnancy. Bass [13b] expresses the opinion that if the infection occurs in the first trimester the risk of congenital deformity is between 25 and 50%, while Ingalls and Purshottam [18] offer the lowest estimate figure of 17%.

From the standpoint of the mother the disease is a trivial affair. It is the tragedy of the pattern of major deformities that arouses our feelings. The incidence of congenital deformities bears no relation to the severity of the disease in the mother. Further, we are now aware of the fact that the mother's infection may be so light as to be entirely missed, yet the infant may have the characteristic deformities, the evidence of rubella resting only on the history of exposure in the first trimester. This possible danger should not be overlooked.*

There can no longer be any doubt that there is a real risk of major congenital deformities as a result of a maternal infection with rubella during

* Schick [20] has speculated on this possibility in mothers who show no symptoms of the disease as a result of an acquired immunity from a previous attack. During a big epidemic year of rubella it is very possible that congenital deformities conforming to the rubella pattern, yet attributed to some other disease acquired during pregnancy, may well be due to a silent rubella infection. This possibility is not in evidence, however, in the seasonal incidence of patent ductus arteriosus and maternal rubella, as regards those with a negative history of the disease in the study of Rutstein et al.[21]

the early months of pregnancy. One may take an optimistic view on the basis of the number of normal babies born in spite of known maternal infection. On the other hand, experience with such major deformities tends to make one pessimistic. The social side is very striking. A blind and deaf baby with a microcephalic head is a terrific strain on the mother and may lead to a relative neglect of the other children. Furthermore, it has been shown very definitely to deter the parents from having any more children. If in early pregnancy one is faced with the possibility of such a family calamity, then from the sociological and preventive medicine standpoint it would appear wise to empty the uterus, and thereby allow a fresh pregnancy to begin under more auspicious circumstances. Unfortunately, there are often religious as well as legal obstacles in the way of therapeutic abortion where the life of the mother is not at stake.

Our newer knowledge of rubella has aroused the interest of the medical world to the question of whether other conditions and other infections during pregnancy can also bring about congenital deformities. The answer is that other agents do seriously affect the fetus. This has been conclusively shown in animal experimentation with vitamin A deficiency,[22] diabetes,[8, 13] drugs and steroids,[23a] and even to the point where exposure to x-ray [23b] at a certain time brings about a constant deformity. It can be stated that no other infectious disease is known to display any such pattern of congenital deformity as rubella. General experience with the common cold, and the evidence in regard to vaccinia [24] and influenza A_1 [11] is sufficient to warrant confidence that these infections are not conducive to congenital deformities. As for other common infections such as streptococcosis,[13] meningococcemia,[10] mumps,[25, 26] measles,[10, 11] chickenpox,[10, 11] herpes zoster,[27] infectious hepatitis,[28, 29] infectious mononucleosis,[27] and poliomyelitis,[30, 3] the answer is that isolated case reports of a variety of deformities are very unconvincing,* and there is insufficient evidence at present to incriminate any of these as being in any way comparable to rubella.[10, 11, 25, 31, 32, 33, 34]

We do not know how rubella happens to have the unique ability to bring about such deformities. It has been suggested that this virus has a peculiar ability to pass through the placenta while others meet a constant barrier in this organ. It has also been suggested that the virus of rubella may affect the placenta and so disturb the nutrition of the embryo. The real point is that if and when maternal rubella does affect the fetus, it is likely to maim seriously rather than to kill, in contrast to other maternal infections, notably relapsing fever and smallpox, and, to a much less extent, many other infections.

What can be done when one is faced with a mother who is exposed to rubella in the first four months of pregnancy? Pooled gamma globulin derived from the Red Cross is low in rubella antibody, just as it is for mumps

* Mumps, chickenpox, infectious hepatitis, and infectious mononucleosis have all been incriminated, but the figures are much too meager to carry any weight.

and chickenpox (and I might make so bold as to add poliomyelitis), in contrast to a relatively high antibody content for measles and infectious hepatitis. Therefore, this gamma globulin cannot be relied on to protect, although theoretically it might do so. Gamma globulin derived from convalescent rubella apparently offers much more likelihood of protection, just as mumps convalescent gamma globulin offers a measurable protection against mumps. A meager supply of convalescent rubella gamma globulin is occasionally on hand at our various serum centers.

The next question is what steps are to be taken in case a mother contracts rubella in the first four months of pregnancy. By the time the eruption appears the virus has probably been circulating in the mother's lymph channels and blood stream. Actually, it has been very difficult to isolate the rubella virus from the blood stream. Nevertheless, the virus presumably reaches the placenta in this way. One can have no confidence in attempting to supply antibodies at this late date with the hope of protecting the fetus. Emptying the uterus is simple in the first three months. Thereafter the operative risk increases with each week. Here again, one may be confronted with religious and legal obstacles. We may look forward to the time when an effective rubella vaccine may be administered as a pre-marital procedure.

BIBLIOGRAPHY

1. Davis, E. P.: Complications of pregnancy, 1924, D. Appleton & Co., New York, p. 78.
2. Anderson, G. W., Anderson, G., Skaar, A., and Sandler, F.: Poliomyelitis in pregnancy, Am. J. Hyg. **55**: 127–139 (Jan.) 1952.
3. Horn, P.: Pregnancy complicated by anterior poliomyelitis. Experience in Los Angeles County Hospital with report of 180 consecutive cases, Ann. West. Med. and Surg. **5**: 93–108 (Feb.) 1951.
4. Weinstein, L., Aycock, W. L., and Feemster, R. F.: The relation of sex, pregnancy and menstruation to susceptibility in poliomyelitis, New Eng. J. Med. **245**: 54–58, 1951.
5. Omar, El Sayed: Rare complications of louse borne relapsing fever, J. Egyptian Pub. Health Assoc., Special Number, Nov. 1946, 195.
6. Rolleston, J. D., and Ronaldson, G. W.: Acute infectious diseases, 1940, C. V. Mosby Company, St. Louis, pp. 392, 319.
7. Marsden, J. P., *in* Banks, H. S.: Modern practice in infectious fevers, 1951, P. B. Hoeber, Inc., New York, Vol. 2, p. 579.
8. Bull, C.: The effect on the fetus of diseases of the mother during pregnancy, Arch. Pediat. **62**: 289–299, 1945.
9. Vaughan, J. E., and Ramirez, H.: Coccidioidomycosis as complication of pregnancy, Calif. Med. **74**: 121–125 (Feb.) 1951.
10. Brandeberry, K. R., and Vergon, J. M.: Meningococcic meningitis in term pregnancy, Am. J. Obst. and Gynec. **61**: 699–700 (March) 1951.
11. Campbell, W. A. B.: Influenza in early pregnancy; effects on foetus, Lancet **1**: 173–174 (Jan. 24) 1953.
12. Greenberg, M., Yankauer, A., Jr., Krugman, S., Osborn, J. J., Ward, R. S., and Dancis, J.: The effect of smallpox vaccination during pregnancy on the incidence of congenital malformations, Pediatrics **3**: 456–467 (April) 1949.
13. Bass, M. H.: (a) Fetal defects resulting from illnesses of the pregnant mother with special reference to virus disease, New York State J. Med. **48**: 1807–1813, 1948. (b)

Diseases of the pregnant woman affecting the offspring, *in* Advances in internal medicine, Dock and Snapper, 1952, Vol. 5, The Year Book Publishers, Inc., pp. 15–58.
14. Hall, E. G., Hay, J. D., Moss, P. D., and Ryan, M. M. P.: Congenital toxoplasmosis in the newborn, Arch. Dis. Child. **23**: 117–124 (April) 1953.
15. Gregg, N. McA.: Congenital cataract following German measles in the mother, Tr. Ophth. Soc. Australia **3**: 35–46, 1941.
16. Swan, C.: Congenital malformations associated with rubella and other virus infections, *in* Banks, H. S.: Modern practice in infectious fevers, 1951, Vol. 2, P. H. Hoeber, Inc., New York.
17. Wesselhoeft, C.: (a) Rubella (German measles), New Eng. J. Med. **236**: 943–950, 978–988, 1947. (b) Rubella (German measles) and congenital deformities, New Eng. J. Med. **240**: 258–261, 1949.
18. Ingalls, T. H., and Purshottam, N.: Fetal risks from rubella during pregnancy, New Eng. J. Med. **249**: 454–455 (Sept. 10) 1953.
19. Collins, I. S.: The incidence of congenital malformations following maternal rubella at various stages of pregnancy, Med. J. Australia **2**: 456–458 (Sept. 19) 1953.
20. Schick, B.: Diaplacental infection of the foetus with the virus of German measles despite immunity of the mother. Analogous observations in smallpox, Acta Pediat. **38**: 563–568, 1949.
21. Rutstein, D. D., Nickerson, R. J., and Heald, F. P.: Seasonal incidence of patent ductus arteriosus and maternal rubella, Am. J. Dis. Child. **84**: 199–213 (Aug.) 1952.
22. Warkany, J.: Congenital anomalies, Pediatrics **7**: 607 (May) 1951.
23. Hicks, S. P.: (a) Developmental brain metabolism, A. M. A. Arch. Path. **55**: 302–327 (April) 1953. (b) Developmental malformations produced by radiation, Am. J. Roent., Radium Therapy and Nuclear Med. **69**: 272–293 (Feb.) 1953.
24. Bellows, M. T., Hyman, M. E., and Merritt, K. K.: Effect of smallpox vaccination on the outcome of pregnancy, Public Health Rep. **64**: 319–323, 1949.
25. Bowers, D.: Mumps during pregnancy, Western J. Surg., Obst. and Gynec. **61**: 72–73, 1953.
26. Dumont, M.: Infection ourlienne maternelle et malformation foetale, Bull. Féd. soc. gynéc. et obst. **3**: 281, 1951.
27. Dods, L.: Pre-natal paediatrics, Med. J. Australia **1**: 205–211 (Feb. 16), 1952.
28. Roth, L. G.: Infectious hepatitis in pregnancy, Am. J. M. Sc. **225**: 139–146 (Feb.) 1953.
29. Hsia, D. Y. Y., Taylor, R. G., and Gellis, S. S.: A long-term follow-up study on infectious hepatitis during pregnancy, J. Pediat. **41**: 13–17 (July) 1952.
30. Priddle, H. D., Lenz, W. R., Young, D. C., and Stevenson, C. S.: Poliomyelitis in pregnancy and puerperium; experience in Detroit epidemics of 1949 and 1950, Am. J. Obst. and Gynec. **63**: 408–413 (Feb.) 1952.
31. Kaye, B. M., Rosner, D. C., and Stein, I. F.: Viral diseases in pregnancy and their effect upon the embryo and fetus, Am. J. Obst. and Gynec. **65**: 109–119 (Jan.) 1953.
32. Huber, H.: Virusinfektion und Schwangerschaft, Med. Klin. **48**: 1304–1306 (Aug. 28) 1953.
33. Clyde, W. A.: Virus infection during pregnancy as the cause of congenital malformation of the heart, J. M. Ass. Alabama **22**: 131–133 (Nov.) 1952.
34. Logan, W. P. D.: Incidence of congenital malformations and their relation to virus infections during pregnancy, Brit. M. J. **2**: 641–645 (Sept. 15) 1951.

RECENT STUDIES ON THE DIAGNOSIS OF CAT SCRATCH FEVER*†

By SEYMOUR S. KALTER, JAMES E. PRIER, and JOHN T. PRIOR,
Syracuse, N. Y.

WITHIN recent years the clinical syndrome referred to as Cat Scratch Fever, nonbacterial regional lymphadenitis, benign inoculation lymphoreticulosis, etc., is being recognized more frequently. Following its first recognition by Debré [1] and Foshay [2] in 1930, numerous reports have been found in the literature concerning the protean nature of the clinical aspects of this disease.[3-7] Because the combination of lymphadenopathy and low grade fever can mimic so many disease processes, our chief interest in this entity has been centered about an evaluation of the laboratory methods currently considered to be of value in diagnosing cat scratch fever.

The protean nature of the disease often leads to confusion in its diagnosis. As a consequence, it is common practice for the clinician to request a wide variety of laboratory tests. For example, it is not unusual to see cases in which, in addition to a complete blood count, urinalysis, blood culture and lymph node biopsy (material subsequently cultured and inoculated into guinea pigs), the following serologic and skin tests were employed:

Serologic tests: Paul Bunnell
Brucella
Tularemia
Proteus X-19
Streptolysin titer
Lygranum CF and
Typhoid-paratyphoid

Skin tests: Tuberculin
Frei
Histoplasmin
Blastomycin and
Cat scratch

The present report places particular emphasis on the skin test and serologic determinations. The results of skin tests on over 250 patients and 94 "normals" or controls are described. With regard to the latter group, i.e., the controls, little information has previously been available concerning skin

* Received for publication July 23, 1954.
From the Virus Laboratory, Department of Microbiology, and the Department of Pathology, State University of New York, Upstate Medical Center, and Bureau of Laboratories, Department of Health, Syracuse, N. Y.
† Aided in part by grants from the Hendrick's Research Fund and United States Public Health Service.

tests of a presumably normal population. An attempt is also made to analyze the serologic findings from patients with the disease.

Materials and Methods

Subjects: Within the past year more than 250 patients with lymphadenopathy of unknown etiology have been skin-tested for cat scratch fever in this center. Approximately one-half of this group were individuals sent to the laboratory by physicians because of lymphadenopathy associated with a history of a cat scratch. The remaining half were hospitalized patients with lymphadenopathy of unknown etiology. A number of the latter group, such as those suspected of having tuberculosis or neoplasm, were initially subjected to a lymph node biopsy. Following the microscopic report of "probable cat scratch fever" this group was referred for cat-scratch skin tests and serologic examination. Whenever possible, cats from families of those having the disease were skin-tested and bled for serologic studies.

The control group consisted of second year medical students and laboratory technicians. These were carefully questioned as to contact with cats, as well as to any history of a previously unexplained lymphadenopathy.

Skin-Test Antigen: Material for preparation of the antigen was obtained either by aspiration of a node from a known case or by preservation of a portion of the biopsy specimen under sterile precautions. Aspiration is readily accomplished from nodes in which suppuration has occurred by means of a 16 to 18 gauge needle, as much as 50 ml. being obtained in rare instances. In this connection, close coöperation between the clinician and the laboratory is of extreme importance, since at present there is no commercial source of skin-test antigen. Material for skin testing was obtained from several different individuals and kept separately.

All such material was treated in a similar manner, i.e., diluted 1:5 in buffered saline (pH 7.4), and heated for two hours on one day and for one hour the following day at 60° C. Following this period of inactivation the antigen was tested for bacteria by inoculation of thioglycollate media, blood agar plates, guinea pigs and mice. At no time was bacterial contamination encountered. The inactivated material was then dispensed in 25 ml. amounts in rubber-capped, sterile serum vials.

One caution observed was to obtain the antigenic materials from patients with no previous history of jaundice. The possibility of transfer of serum hepatitis virus under these conditions, although not reported to date, must be emphasized.

For skin testing, 0.1 ml. was given intradermally in the forearm and the skin reaction read after 24 to 48 hours. Although several batches of antigen have been employed, as yet no false-positive or false-negative reactions have been observed. A few of the antigen preparations gave strongly positive reactions within 24 hours. There is also some apparent variation in stability among the preparations, since one batch gave strong reactions

after one year whereas another preparation was effective for only about six months.

Any area of erythema, with or without induration, was considered positive. In some instances the skin reaction was more intense than in others, and induration at times was lacking. Readings were made at both 24 and 48 hours because of the delayed reaction of some antigens.

Serology: Complement-fixation tests were performed on sera of both patients and animals, using "Lygranum CF." All sera were inactivated at 56° C. for 30 minutes before testing. Twofold serial dilutions of the serum were made in saline in 0.2 ml. volumes. To these dilutions, 0.2 ml. complement (2 units) and 0.2 ml. antigen (2 units) were added. These mixtures were incubated at 37° C. for 1¼ hours, after which 0.4 ml. sensitized sheep cells were added. The tests were then further incubated for 30 minutes. Appropriate controls were included. Reactions of 2 plus or more were considered positive.

Clinical Observations

The clinical picture of cat scratch fever has been described by numerous workers.[3-7] From the reports in the literature and from the more than 250 patients in the present study it is apparent that the course of the disease is extremely variable. This variability manifests itself not only in the observed clinical manifestations but also in the incubation period, fever, lymphadenopathy and response to skin test. Variability in age susceptibility was also evident, with patients ranging from one to 67 years. The sex distribution was approximately equal.

The incubation period, when dated from the scratch, was usually about two to three weeks. In a few instances the onset was only three to four days after the scratch. There were occasional patients in whom the onset of the disease appeared to be two to three months after cat scratches. However, as will be emphasized below, dating the onset of the disease from the date of scratch may be misleading.

In approximately one-half the patients studied, i.e., in the group that was hospitalized, body temperatures were recorded. There was no consistent pattern in the temperature curves observed. Extreme variability in ranges and duration was noted in a number of individuals. One patient, a 16 year old boy, maintained a chronic low grade fever for two to three months. Several patients, even though hospitalized, were afebrile. Most of the patients referred to us by practicing physicians were afebrile throughout the course of their lymphadenopathy, as far as could be ascertained by questioning.

Lymphadenopathy is a constant feature of the disease. Although this adenopathy is most frequently regional, a generalized adenopathy has been seen in some of our cases. In two patients, hilar nodes have been demonstrated by chest roentgenography. The nodes, whether local or generalized,

are variable in size and in tenderness. In most instances the nodes are quite large, usually about 2 to 5 mm. in diameter. In one patient an axillary node of approximately 15 cm. was observed, and this node yielded approximately 50 ml. of purulent material. The lymph nodes are generally fluctuant and readily palpable, and some patients reported that they were extremely tender. A great number recognized the presence of a node by sight rather than by pain.

Although most nodes became fluctuant and looked as though they would form a cutaneous sinus tract, this occurred in only one patient. (It was a cervical node.) Spontaneous regression usually occurred when the nodes were left undisturbed. At times lymph nodes were found that would repeatedly become enlarged and tender but would eventually disappear. In several instances the lymphadenopathy persisted for a number of months, but the majority resolved in two to three weeks.

Primary lesions were apparent in a number of patients tested. These lesions, usually in the form of a papule, were at the site of the cat scratch. It should also be pointed out that many of the control group gave histories of having been scratched by cats at one time or another but were negative when skin-tested. There were also positive skin-test reactors among the patients who stated that they had neither owned nor had contact with cats. Individuals such as these, when persistently questioned, will usually recall some previous contact such as visiting someone who had cats. It soon became evident that very few people have not at one time or another had direct contact with cats. Inasmuch as cat scratches have been presumably ruled out as absolutely necessary for inciting the disease, it becomes more difficult to evaluate the exact rôle of the cats in the transmission of the disease.

Nonspecific complaints such as nausea, headache, lassitude and malaise were frequently described. The total and differential leukocyte count was usually within normal limits, although several patients showed a 6 to 10% eosinophilia. Some of the latter patients who were subjected to lymph node biopsy disclosed an eosinophilic cell increase within the nodal tissue.

We have not observed any cases associated with encephalitis, although a number have been recorded in the literature.[7-9]

A wide variety of chemotherapeutic agents have been employed in attempting to alleviate the clinical symptoms and to shorten the course of the disease, but none has proved to be effective.

Skin Test

More than 250 patients with lymphadenopathy of unknown etiology were tested with antigen prepared from material obtained from the nodes of several different patients with cat scratch disease. In addition, a control group of approximately 94 individuals was also skin-tested. The results are given in table 1. The reactions obtained with the different antigens

were generally similar. Variation due to different antigens occurred in (1) time of reading, i.e., some antigens produced reactions readable in 24 hours, others could not be read before 48 hours; (2) intensity of skin test, i.e., the areas of erythema varied with the lot of antigen, as well as with the individual patient; and (3) stability of antigen. Induration was usually but not always present. Doubtful readings were occasionally observed in the form of an extremely small area of erythema, about 1 or 2 mm. in diameter.

Of the 250 patients studied, 210 (84%) were positive, 15 (6%) were doubtful and 25 (10%) were negative. Of the 25 negative patients, 18 were subsequently shown to be patients with a lymphadenitis, usually bacterial in origin, which responded to chemotherapy. The remaining seven of the cat scratch skin-test negatives were later proved to be neoplastic. Of the 210 positive reactors, 135 (60%) gave a definite history of having been

TABLE 1

Skin Reactions to Cat Scratch Antigen in a Population

Total No. Tested	Skin Test Reactions	No.	%	Scratched by Cats		Intimate Contact with Cats		No Known Contact with Cats		Adenopathy	
				No.	%	No.	%	No.	%	No.	%
Patients 250	Positive	210	84.0	135	65.0	70	33.0	5	2.0	210	100
	Negative*	25	10.0	5	20.0	15	60.0	5	2.0	25	100
	Doubtful	15	6.0	15	100.0	—	—	—	—	15	100
Controls 94	Positive	3	3.2	2	66.7	1	33.3	—	—	—	0
	Negative	83	88.3	56	67.5	7	8.5	20	24.0	—	0
	Doubtful	8	8.5	6	75.0	1	12.5	1	12.5	—	0

* Clinical picture suggested cat scratch fever. Several were patients with abscesses or other pathologic conditions (proved later).

scratched by cats. All (or 100%) of the 15 doubtful skin-test reactors claimed to have been scratched, whereas five (20%) of the 25 negative skin reactors recalled cat scratches. When the patients who had not been scratched by cats were questioned regarding any possible contact, 70 of these either owned cats or were knowingly in close association with cats. Thus, of the 210 positive skin-test patients, 205 (98%) had either been scratched by or were associated with cats. Only five (2%) of the positive reactors could not recollect any association (even remotely) with cats. Whether these can be considered to be false-positives is open to speculation. All of the 15 doubtful patients had been scratched by cats. Of the 25 patients in the negative group, five had been scratched, 15 had been in contact with cats, and five could not recall any contact with cats.

A control group consisting of second year medical students and laboratory personnel was also skin-tested to study the results of skin reactions in a presumably normal population. There were 94 individuals in this control

group. History of contact with cats among individuals within this control group was similar to that of the patients. In most instances, contact with cats could be elicited from most of the individuals. Of the 94 control individuals, all but 21 had either been scratched or been in close association with cats for some period of time. These 21 persons were unable to recall any contact with cats at all. Of the control group, 83 (88.3%) were negative to the skin test. There were three positive (3.2%) and eight doubtful (8.5%) reactors to this same skin test. Two of the three positives had been scratched by cats in the past (one permanently scarred), and six of the eight doubtfuls had been scratched. No history of a past adenopathy was obtained in the control group. However, in view of the mild lymphadenopathy observed in several patients, a failure to recall such a condition during one's lifetime is not improbable.

TABLE 2

Results of Complement Fixation Tests with "Lygranum CF" Antigen; Sera from Patients and Cats

No. Sera (Patients)	No. Negative	Complement-Fixing Titers (Positives)					
		1:5	1:10	1:20	1:40	1:80	1:160
Single 20	10	4	1	1	2	1	1
Paired 2*	0	1. A x	—	—	—	—	—
		B x	—	—	—	—	—
		2. A x	x	x	—	—	—
		B x	x	x	x	x	—
Cats 4	4	—	—	—	—	—	—

* The two paired sera were obtained approximately two weeks apart. A = acute phase, B = convalescent phase. Both patients were ill several weeks prior to the obtaining of the "acute" specimen.

SEROLOGY

The serologic data are presented in table 2. Complement fixation tests were performed with "Lygranum CF" antigen on 20 single human sera taken late in the course of illness, two pairs of acute and convalescent sera and four cat sera. In addition, attempts were made to use either aspirated necrotic lymph node material or the lymph node itself as a complement-fixing antigen. The procedure for the complement fixation test has been given above.

Of the 20 single sera tested for complement-fixing antibodies, 10 had no titer whatsoever and the remaining 10 had varying titers. The range of titers is given in table 2. Of the paired sera, one individual showed no antibody rise after approximately two weeks' illness. The titer with "Lygranum CF" was 1 : 5 in both instances. However, the other patient's

titer increased from 1:20 to 1:80, a fourfold increase. All the cats' sera were negative. These cats were domestic pets of patients with cat scratch fever and were clinically normal animals.

Histopathology

The following observations are based on the microscopic study of lymph node tissue from between 30 and 40 definitely proved cases of cat scratch fever. Although the most frequently biopsied group of nodes has been the axillary, nodes have been examined from the cervical, epitrochlear, inguinal, parotid and occipital areas.

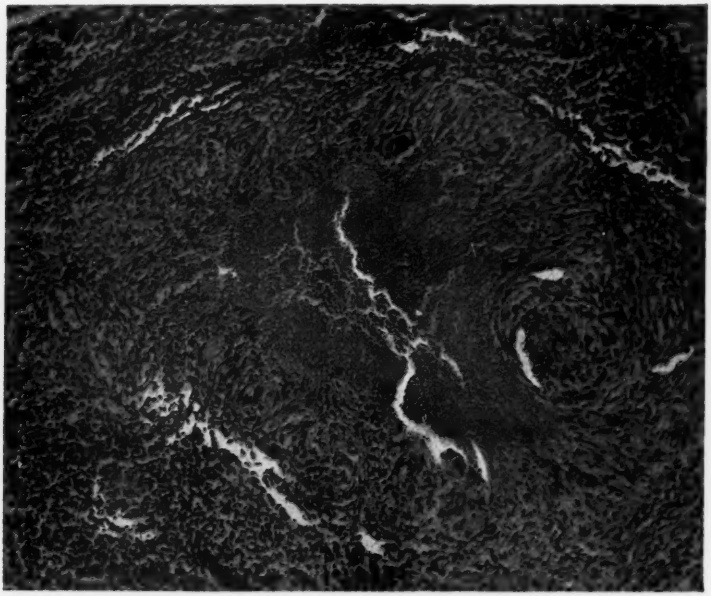

Fig. 1. Tuberculoid reaction with central caseation, broad zone of epithelioid cells and some giant cells. × 127.

It is of interest that while the operating surgeon invariably had the impression he was removing a solitary enlarged lymph node, it was subsequently noted on microscopic examination that the solitary mass was actually a fused group of moderately enlarged nodes. The gross appearance of the tissue was generally nonspecific, and the submitted specimens varied from multiple small fragments of soft, reddish gray, necrotic nodal and sinus tract tissue to encapsulated, rather firm masses averaging around 2.5 cm. in diameter. The latter were pearl gray on section, and frequently 0.1 cm. white, necrotic nodules were identified beneath the capsular surface. Frag-

ments of nodal tissue were usually preserved under sterile precautions for bacteriologic examination.

Although it must be emphasized that the histopathology of cat scratch disease is nonspecific, certain characteristics are seen frequently enough to be of definite value in the diagnosis of this condition. Capsular thickening with marked chronic inflammatory cell reaction was constantly present. Not infrequently, large numbers of eosinophils were noted among the capsular lymphocytes and plasma cells, and giant cells of the Langerhans type were sometimes observed. Varying degrees of enlargement of the cortical lymph nodules and their germinal centers were present. The remainder

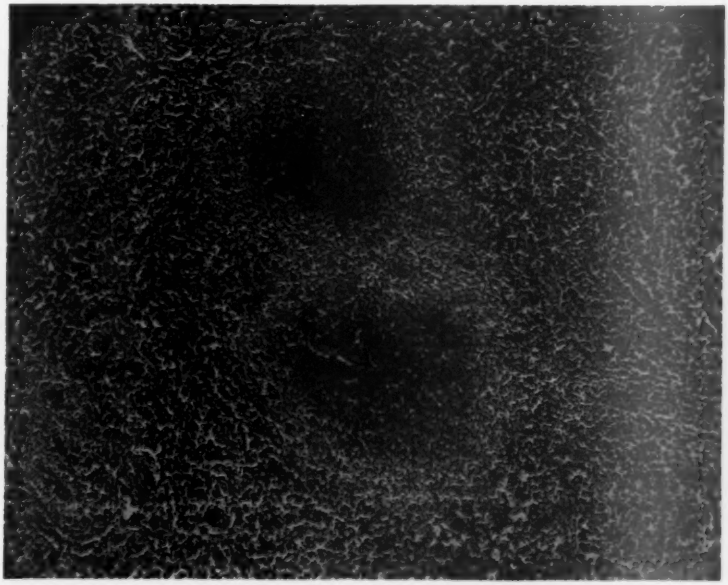

FIG. 2. Two granulomata, with central foci being composed of necrotic polymorphonuclear leukocytes. A poorly defined epithelioid cell layer blends with the congested medullary cords and sinuses. × 66.

of the histopathologic picture was both cortical and medullary in location, and may be grouped according to one of three patterns, although admixtures of the various types were sometimes observed:

1. Acute caseous
2. Acute necrotizing
3. Epithelioid cell

The caseous variety, in our experience, has been the most commonly observed. This type of lesion is the classic "soft" tuberculoid granuloma,

composed of a large central eosin-staining amorphous caseous material about which there is a peripheral zone of epithelioid cells (figure 1). The latter were mononuclear in type, with large vesicular nuclei and scant acidophilic cytoplasm. Many of these cells showed evidence of degenerative changes, and lymphocytes were scattered throughout this zone. Multinucleated giant cells of the Langerhans variety were constantly present within the epithelioid cell zone. Inclusion bodies were not noted within the giant cells. A thin rim of lymphocytes often delineated the margins of these granulomata. The caseous foci tended to fuse with adjacent similar areas, and they frequently

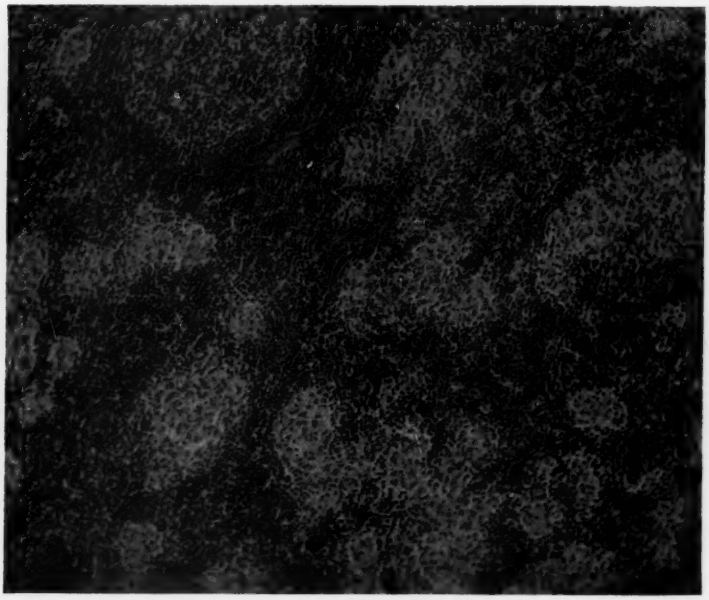

FIG. 3. Epithelioid cell granulomata, showing tendency for fusion of adjacent granulomata. An active germinal center is present in the upper left corner. × 127.

extended through the capsule. Acid-fast stains to demonstrate the presence of tubercle bacilli have been consistently negative. It must be pointed out, however, that this type of lesion cannot be differentiated on a histologic basis from the classic reaction to the tubercle bacillus, and it is our impression that many of the cases of cat scratch disease have in the past been misdiagnosed as tuberculosis, presumably bovine.

The acute necrotizing type differed from the first variety chiefly in that the core, instead of being caseous, consisted of a central focus of polymorphonuclear leukocytes showing marked pyknosis and karyorrhexis (figure 2). A well defined epithelioid cell layer was not present, the necrotic

material blending imperceptibly with the medullary cords and congested medullary sinuses. Giant cells were very seldom seen in association with this type of reaction. Fusion of adjacent necrotic granulomata and extension into the capsular tissue were common. It can be appreciated that this reaction is actually a nonspecific suppurative lymphadenitis and corresponds rather closely to the microscopic pattern seen in cases of tularemia, lymphogranuloma venereum and brucellosis.

The last variety, the epithelioid cell, was composed of collections of epithelioid cell granulomata of varying sizes which showed marked tendency

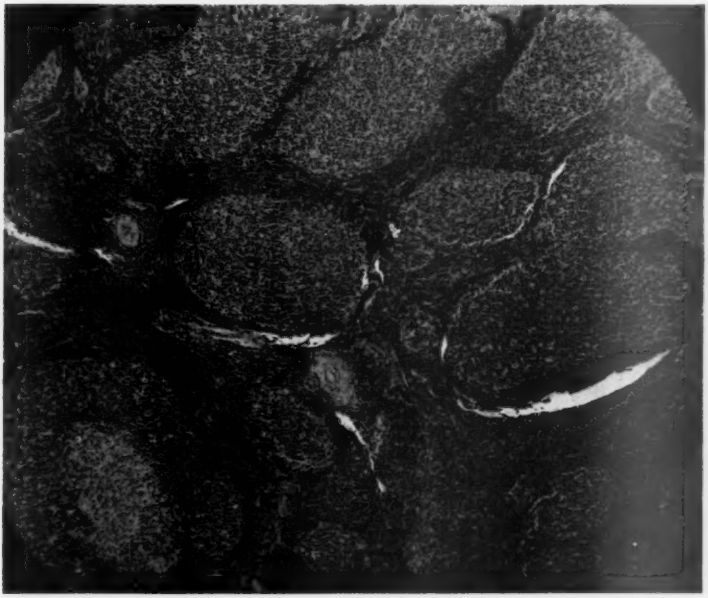

FIG. 4. Follicular hypertrophy and germinal center hyperplasia. A small epithelioid cell granuloma is present in the lower left corner. × 60.

towards fusion (figure 3). The individual cells were large and contained vesicular nuclei, prominent acidophilic nucleoli and abundant cytoplasm. Langerhans' giant cells without inclusions were infrequently observed. The granulomata showed no evidence of caseation or significant cellular degeneration, and this picture was indistinguishable from Boeck's sarcoid, with which many of our cases early in this study were confused. It is significant that the most marked germinal center hyperplasia was noted in association with this histologic type of cat scratch disease, and rare cases were initially considered on the basis of the biopsy specimen to be instances of giant follicular lymphoma (figure 4). Careful study of the nodal pattern, however,

disclosed the minute granulomata and phagocytic cell activity which are not associated with the histopathology of this type of lymphoma.

Discussion

The recognition of cat scratch fever as a clinical entity is well established. A previous report from this laboratory has emphasized the protean nature of the clinical picture.[5] This report describes the clinical variation as seen in more than 250 patients. The rôle of the skin test as an aid to diagnosis is described.

From the results reported herein, it would appear that the skin test is of primary diagnostic value. This is substantiated by the findings obtained when a control group of normal individuals was also skin-tested. Although the relationship of skin-testing antigen to the etiologic agent still remains obscure, the specificity appears to be fairly accurate.

Many individuals apparently are scratched by cats, or at least are intimately associated with them, and are negative skin reactors. What, therefore, is the relationship of the cat to the disease? It would appear that not all cats are carriers of the agent (or agents) causing this syndrome. It would also seem that they may be mechanical carriers, inasmuch as they do not demonstrate detectable antibodies when tested against "Lygranum CF." The cats also appear to be healthy, at least as far as physical appearance is concerned. Complete necropsy studies of several of these animals failed to show significant abnormalities. The rôle of inapparent infection, however, has yet to be elucidated.

We have studied a number of cats in an attempt to isolate an etiologic agent. Various tissues from these cats have been passaged in several laboratory animals, without success. The etiology of this disease therefore remains obscure. The serologic relationship to the lymphogranuloma venereum-psittacosis group is highly suggestive. The difficulties in isolating an agent again substantiate this lack of relationship. Investigation into the etiology of this disease is being continued.

Summary

The problems involved in making a diagnosis of cat scratch fever have been presented. The skin test using an antigen prepared from materials obtained from lymph nodes of patients with the disease appears to be the best available diagnostic procedure at present. This conclusion is substantiated by the results of skin-test studies on a large number of cases of cat scratch disease and normal controls. The serologic examination and the histopathology of the biopsied node, although suggestive, can in no way be considered specific. In the presence of a history of contact with cats, especially a history of a cat scratch, and a positive skin test, biopsy of an affected enlarged lymph node is not considered essential for the establishment

of the diagnosis of cat scratch fever. The etiology of this disease remains obscure, as does its relationship to the lymphogranuloma venereum-psittacosis group. Caution in the use of antigenic material for skin testing from patients with a history of jaundice is emphasized.

ACKNOWLEDGMENTS

The able technical assistance of Miss Lee Herman is appreciated. We also wish to thank Dr. L. Berman, Dr. W. Michaels and Dr. W. Waters, and the Class of 1956 (State University of New York, Upstate Medical Center at Syracuse) for their coöperation.

BIBLIOGRAPHY

1. Debré, R., Lamy, M., Jammet, M. L., Costil, L., and Mozziconacci, P.: La maladie des griffes de chat, Bull. et mém. Soc. méd. d. hôp. de Paris **66**: 76–79, 1950.
2. Foshay, L.: Personal communication.
3. Editorial, Cat-scratch disease, J. A. M. A. **148**: 746, 1952.
4. Daniels, W. B., and MacMurray, F. G.: Cat scratch disease; nonbacterial regional lymphadenitis: a report of 60 cases, Ann. Int. Med. **37**: 697–713, 1952.
5. Waters, W. J., Kalter, S. S., and Prior, J. T.: Cat-scratch syndrome, Pediatrics **10**: 311–318, 1952.
6. Daeschner, G. W., Salmon, G. W., and Heys, F. M.: Cat-scratch fever, J. Pediat. **43**: 371–384, 1953.
7. Daniels, W. B., and MacMurray, F. G.: Cat-scratch disease. Report of 160 cases, J. A. M. A. **154**: 1247–1251, 1954.
8. Stevens, H.: Cat-scratch fever encephalitis, Am. J. Dis. Child. **84**: 218–222, 1952.
9. Thompson, T. E., and Miller, K. F.: Cat-scratch encephalitis, Ann. Int. Med. **39**: 146–151, 1953.

HYPNOTIC EFFECTS OF AN ANTIHISTAMINE—METHAPYRILENE HYDROCHLORIDE*

By Bernard Straus, M.D., F.A.C.P., Julius Eisenberg, M.D., and Joseph Gennis, M.D., F.A.C.P., *New York, N. Y.*

It is widely recognized that one of the important side effects of the antihistamines as a class is their sedative action; it has also been considered the most characteristic.[1] Controlled studies of their hypnotic (sleep-inducing) effect, however, are lacking. This side effect may be either desirable or objectionable, depending on the situation in which the drug is employed. It was obvious that such a side effect might be used to good advantage as a primary action, i.e., the use of antihistamines as hypnotics. This would seem to be of some value, since the toxicity of this class of compounds is low. Despite the fact that adequate evidence of their value as hypnotics is not available, the antihistamines have been used widely for this purpose. Indeed, some antihistamines, e.g., methapyrilene hydrochloride, are advertised extensively to the public and sold in large quantities for their hypnotic effect since, unlike other hypnotics such as the barbiturates, they may be dispensed without prescription. Inasmuch as the sedative effects of different members of this large class of compounds are extremely variable,[2] it seemed desirable to perform a controlled study of one of the compounds which is advertised and used for its hypnotic effect. Methapyrilene hydrochloride (Histadyl, Dormin, Thenylene Hydrochloride) was selected for this purpose.

In a study of this compound, by Feinberg and Bernstein,[3] sedation was a common finding, occurring in 48 (or 19%) of 253 patients, most of whom received 50 mg. doses. The degree of sedation was not so great as that produced by Benadryl, but approximated or perhaps exceeded that experienced with Pyribenzamine. Friedlaender and Friedlaender[4] noted drowsiness in 13 of 117 patients with 100 mg. doses. Kierland and Potter[5] reported that 10 of 126 patients experienced drowsiness with this drug on doses of 100 mg. three to four times daily. Most authors have reported minimal and infrequent toxic effects with methapyrilene. These have consisted of vertigo, nervousness, dryness of the mouth and throat, excitation, insomnia, headache, nausea and diarrhea.

Methods

Patients for this study were chosen from the Medical Service of the Veterans Administration Hospital, Bronx, N. Y. (table 1). It was re-

* Received for publication April 27, 1954.
From the Medical Service, Veterans Administration Hospital, Bronx, N. Y. This study was aided by a grant from the Food and Drug Administration.

quired that each have a sleep disturbance as manifested by a continuing need during hospitalization for a hypnotic (table 2). No patient was accepted for the study who had acute physical symptoms which significantly disturbed sleep, was a known placebo reactor, exhibited a severe emotional disturbance or required narcotics.

In the event one of these contraindications arose during the study, the night's observation involved was discarded and repeated, or the patient was eliminated from the study.

TABLE 1

Primary Diagnosis		Number of Patients
Cardiovascular disease		20
Arteriosclerotic	12	
Rheumatic	3	
Hypertensive	3	
Luetic	1	
Beriberi	1	
Peptic ulcer		8
Portal cirrhosis		4
Hepatitis—viral		4
Diabetes mellitus		2
Pulmonary tuberculosis		2
Chronic bronchitis with emphysema		2
Scleroderma		1
Pernicious anemia		1
Diverticulosis (colon)		1
Peripheral neuritis		1
Tuberculous meningitis		1
Hodgkin's disease		1
Regional enteritis		1
Amebiasis		1
Thyrotoxicosis		1
Rheumatoid spondylitis		1
Bronchogenic carcinoma		1
Thrombophlebitis		1
		54

TABLE 2

Duration of Sleep Disturbance Prior to Hospitalization	Number of Patients
12 months or more	28
From 6 to 12 months	5
From 1 to 6 months	3
For 1 month	5
Undetermined length of time	2
	43
Disturbed sleep since hospitalization only	11
	54

All of the 54 subjects so selected and studied were males. The average age was 52.2 years.

Methapyrilene hydrochloride (50 mg.), phenobarbital (100 mg.), and a placebo were administered as capsules of identical appearance. Although the investigators were aware that these three agents were under study, they had no knowledge of the specific contents of a particular capsule. The capsules were labeled "A," "B" and "C."

The study was designed to give each of these three compounds six times to each patient during a three week period. For various reasons, it was not possible to adhere to such a schedule in all instances. However, an average of 17 observations per patient was obtained, approximately equally divided among the three agents.

To help validate the comparative evaluation, a method of randomization was employed which permitted each agent, in turn, to be preceded and followed, on successive nights, by a second agent.[6] A different sequence of administration was used for each patient.

The response to each medication was evaluated objectively and subjectively by the nurse and patient, respectively. Each category was graded as poor, fair, good or excellent. A special nurse was employed to distribute the appropriate capsules to each patient at the hour of sleep. She then observed him at hourly intervals during the night by directing a flashlight above the bed while standing at the bedside. Her observations were recorded in the listed categories and all categories were graded. The following day, a physician independently elicited the subject's own grading of these same categories. The interviews were conducted by the same physician throughout the study. As a rule, neither the nature of the medication nor any aspect of the study was discussed with the patient. However, in some instances it was necessary to identify the capsules as "sleepers." All comments and information were carefully phrased in a neutral and noncommittal manner. As one might anticipate, because of the time of administration and the nature of the daily interviews, all subjects eventually assumed that the medication was given to promote sleep. At no time, however, was there any indication that any patient was aware of the true, i.e., comparative nature of the study.

Results

To evaluate the hypnotic effect of the three unknown compounds our data were quantitated, classified and analyzed using standard statistical methods. Three criteria of response—falling asleep, staying asleep and over-all evaluation—were obtained from two sources, the patient and the nurse. Six groups of data for each compound were obtained. To quantitate the responses a scoring system was used: Score 0—no sleep response; Score 1—slight sleep response; Score 2—good sleep response; Score 3—excellent sleep response. The percentile response for each score is shown in table 3.

The following procedure was used to determine which of the unknown compounds was effective as a hypnotic. For each patient, the average score of each compound was calculated. These average scores were then compared as responses of the individual to the three unknown compounds expressed in percentages. These comparisons were made for each patient. Table 4 lists the number of patients who showed higher average scores with

one compound than with the other in each of the comparisons. In analyzing these comparisons the probability of chance occurrence of these differences in response was determined by applying an exact binomial test. The probability levels are listed in table 4 for each of the comparisons. Where the level of probability is small, that is, less than 0.05, it can be concluded that the differences in response are significant.

The greatest differences in patient response occurred between compounds A and C, and A and B. The difference in response between B and

TABLE 3

Per Cent Response for Each Score, by Compounds

Criterion	Evaluator	0	1	2	3
		A			
Falling asleep	Patient	34.6	10.5	15.4	39.5
	Nurse	11.4	13.3	14.3	61.0
Staying asleep	Patient	16.1	22.7	23.4	37.8
	Nurse	5.8	11.0	29.7	53.5
Total evaluation	Patient	24.3	27.0	36.5	12.2
	Nurse	5.9	14.0	32.2	47.9
		B			
Falling asleep	Patient	26.9	10.2	20.7	42.2
	Nurse	13.6	10.5	16.3	59.7
Staying asleep	Patient	7.5	19.3	29.2	44.1
	Nurse	4.7	12.8	26.0	56.4
Total evaluation	Patient	15.4	22.9	44.4	17.4
	Nurse	4.8	16.0	29.4	49.8
		C			
Falling asleep	Patient	24.7	10.3	18.6	46.5
	Nurse	6.7	10.9	16.3	66.0
Staying asleep	Patient	12.0	22.0	23.3	42.7
	Nurse	4.2	9.9	23.7	62.2
Total evaluation	Patient	19.0	23.8	39.9	17.4
	Nurse	5.1	9.9	30.4	54.5

C was less significant. It was therefore concluded that compound A was probably the placebo and compounds B and C represented drugs with hypnotic effect.

It may be stated at this point that compound A was the placebo, compound B was phenobarbital, and compound C, methapyrilene. These facts were disclosed to the investigators only following completion of the study.

Comparison of methapyrilene (C) with placebo (A): The data in each

of the six categories make it apparent that methapyrilene has a greater hypnotic effect than the placebo, which is statistically significant. The six levels of probability range from P = .003 to P = .056.

Comparison of phenobarbital (B) with placebo (A): With respect to the criteria staying asleep and over-all evaluation, the data clearly indicate that phenobarbital had a greater hypnotic effect than the placebo. The response to falling asleep with phenobarbital yielded a probability level of

TABLE 4

Criterion	Evaluator	No. of Patients Responding			Level of Probability (P)
		Higher on Compound	Higher on Compound	Tie	
		A	C		
Falling asleep	Patient	18	31	5	.043
	Nurse	16	32	6	.015
Staying asleep	Patient	14	34	6	.003
	Nurse	18	30	6	.056
Total evaluation	Patient	15	28	11	.033
	Nurse	17	29	8	.052
		A	B		
Falling asleep	Patient	20	29	5	.126
	Nurse	23	20	11	.729
Staying asleep	Patient	13	32	9	.003
	Nurse	23	26	5	.388
Total evaluation	Patient	12	34	8	.001
	Nurse	24	25	5	.500
		B	C		*
Falling asleep	Patient	22	26	6	.666
	Nurse	16	29	9	.072
Staying asleep	Patient	28	19	7	.242
	Nurse	19	26	9	.372
Total evaluation	Patient	35	17	2	.008
	Nurse	21	28	5	.392

* Two-tailed test.

P = 0.126. This suggests that there may be a greater effect from phenobarbital than from the placebo, but this is not conclusive. This result is in accord with the known pharmacologic action of phenobarbital, whose effect is slow in onset. In no case did the nurse's evaluation show a significant effect due to phenobarbital.

Comparison of methapyrilene (C) with phenobarbital (B): In comparing methapyrilene or phenobarbital with the placebo the probability levels

used were based on one-tailed tests. This is a statistical device to determine whether a drug is more effective than a placebo. In comparing methapyrilene with phenobarbital, since either drug may be better than the other the probability of chance occurrence is doubled. To determine the statistical significance of differences, a two-tailed test, or a doubling of the calculated probabilities, is involved. Based on the falling-asleep criterion, patients could not distinguish between methapyrilene and phenobarbital, while the evidence suggests that the nurse could distinguish between them, and found methapyrilene more effective. For the staying-asleep criterion, the patient and nurse could not distinguish between the two compounds. In the over-all evaluation the patients indicated that phenobarbital was more effective than methapyrilene, while the nurse could not distinguish between them.

In analyzing data of this type a basic problem involves the method of classification of the scored data into valid and sensitive comparisons between the compounds. Three other statistical procedures were applied to our data but were found to be less sensitive in the determination of differences among the compounds than the method finally selected.

This analysis of our data indicates that both methapyrilene and phenobarbital were more efficient than the placebo in their hypnotic effect. The patients' over-all evaluation favored phenobarbital, and the nurse's observations revealed that methapyrilene was more effective than phenobarbital in inducing sleep.

Discussion

Sleep is a physiologic state which embodies, in intimate conjunction, psychic phenomena and physical factors. It is generally recognized that emotion, fatigue, pain and visceral sensations all play a rôle in the induction and maintenance of the process of sleep. The perception of the depth and the duration of the sleep experience similarly is colored or distorted in the mind of the subject by health or illness, by dreams, by his environment and by his affect or kvale (feeling state). The appreciation and evaluation of sleep by the patient are modified also by such considerations as the amnesia characteristic of deep or dreamless sleep, and the sensations associated with a dream or nightmare. For these reasons, self-evaluation of a night's sleep is characterized by many vagaries and contradictions. Statements by individuals concerning sleep experiences are notoriously unreliable. The person whose snoring has shaken the rafters and roused the neighbors will often blandly assert (and believe) that he slept not a wink all night.

However, to have employed trained subjects with keener perceptions in the realm of self-analysis and observation, as has been done in the evaluation of the pain experience, would have been open to the same criticism, i.e., that artificial conditions were created which could not be related to general experience. This would have vitiated an essential purpose of this study, which was to evaluate the test compound under clinical conditions.

Objective evaluation by an observer is equally difficult. In the absence of precise methods of analysis, the objectivity of an observer is limited. In many instances the observer is unable to determine with any degree of certainty whether a person is asleep. In some individuals, regularity and depth of respiration, flushing, sweating, snoring, drooling or an open mouth suggests sleep. Unfortunately, these manifestations are too inconstant to be of great value in any experiment designed to measure the hypnotic qualities of a compound. Electroencephalography recommended itself because characteristic wave patterns are produced during sleep. However, it was felt that the apparatus involved would introduce disturbing factors which in themselves would be difficult to evaluate. Similar considerations governed the discarding of such procedures as bell rings, light flashing, and electric or touch stimulation. Another objection is the thought that sleep is essentially a subjective experience. This view would suggest that, inasmuch as there are no precise methods for the mensuration of the state of sleep, the important element is not sleep but the memory or impression of sleep. This represents an idealistic approach to a physical state whose acceptance by the physiologist is difficult. Limitations of methods should not result in abandoning the attempt to achieve a degree of objectivity.

It is clear that proper evaluation of the character of an individual sleep experience is fraught with great difficulty, and at times is impossible under the best of conditions. In this, sleep is akin to such subjective responses as pain or pleasure. It was decided to employ both an objective and a subjective method. This involved hourly observations of the patient by a competent observer, and appraisal of the subjective reaction of the patient in a neutral interview. The problems involved were minimized by the use of the double blind test, in which neither the observer nor the subject was aware of the nature of the medication employed, by proper randomization, and by use of a standard of reference (phenobarbital) and placebos. The patient served as his own control. These methods have been discussed by Beecher [6] in his admirable paper on the measurement of the subjective response.

The statistical validation of the hypnotic effects of the antihistamine employed in this study is apparent. In a dose of 50 mg. the antihistamine compares favorably with phenobarbital in the standard dose of 0.1 gm. In any study of a subjective response the placebo reactor represents a significant problem and may dilute the data obtained. Although all known placebo reactors were excluded from the study, it was found that over 30% of the patients scored the placebo as excellent in inducing and maintaining sleep. This high percentage is in accord with the experience of others [6] in the evaluation of any subjective response. Despite this high general incidence of placebo reactors, the methods employed permit a statistically valid statement of the relative merits of the three compounds.

The demonstration that an antihistamine of low order of toxicity is

comparable as a hypnotic to phenobarbital in standard dosage is important. Barbiturates not only have significant toxicity but may also create dependency. Habituation to the barbiturates is common. Suicide and accidental poisoning with overdosage of barbiturates represent a significant hazard. Moreover, barbiturates may be contraindicated in the presence of liver or renal disease. However, the antihistamines, contrary to popular belief, also present dangers with regard to toxicity. Two cases of death due to poisoning following methapyrilene hydrochloride overdosage have been reported. One was a successful suicidal attempt,[7] and the other was due to accidental ingestion by a child.[8] Both patients died in convulsions. Toxic reactions (excluding drowsiness) have been noted in approximately 14%. These have consisted chiefly of dizziness, nausea, vomiting, headache, insomnia, urinary difficulty and nervousness.[5] Certain antihistamines may produce granulocytic hypoplasia. These are the phenothiazine type (Phenergan), which carries a moderate risk, and the ethylenediamine type (Pyribenzamine and methapyrilene), which has a low risk.[9] While we are not aware of any cases of agranulocytosis due to methapyrilene hydrochloride, it is possible that the widespread use of this compound will result in such a complication, and the necessary precautions must be observed. In this study, no toxic effects following the use of any of the agents employed were observed. However, it is emphasized that methapyrilene was administered intermittently and only for a short period of time. It is to be expected that prolonged use will result in a higher incidence of complications.

Another objection to the use of an antihistamine as a hypnotic is the tendency to develop tolerance for the sedative action, sometimes after the first few doses of the drug.[1]

Summary and Conclusions

1. A controlled study of 54 patients compared the hypnotic effects of an antihistamine, methapyrilene (50 mg.), with phenobarbital (0.1 gm.) and a placebo.

2. Methapyrilene and phenobarbital exhibited a greater hypnotic action than the placebo.

3. The hypnotic effects of methapyrilene and phenobarbital were approximately equal.

4. No toxic effects due to methapyrilene were observed in this short-term study. However, since methapyrilene is an antihistamine of the ethylenediamine type, it may produce agranulocytosis, and proper precautions must be taken in its use, especially when it is administered for long periods of time.

Acknowledgment

The authors wish to express their appreciation to Mr. William Weiss, of the Food and Drug Administration, for his statistical analysis of their data.

BIBLIOGRAPHY

1. Feinberg, S. M., Malkiel, S., and Feinberg, A. R.: The antihistamines, 1950, Year Book Publishers, Chicago.
2. Landis, C., and Zubin, J.: The alleged sedative effect of thonzylamine hydrochloride (Neohetramine), J. Lab. and Clin. Med. **38**: 873–880, 1951.
3. Feinberg, S. M., and Bernstein, T. B.: Histamine antagonists. VIII. N-(a-Pyridyl)-N-(-Thienal)-N′,N-Dimethylethylenediamine, a new anti-histaminic compound. Experimental and clinical experiences, J. Lab. and Clin. Med. **32**: 1370–1373, 1947.
4. Friedlaender, A. S., and Friedlaender, S.: Antihistaminic, antianaphylactic and antiallergic activity of N-(a-Pyridyl)-N-(a-Thenyl)-N′,N′-Dimethylethylenediamine hydrochloride, Am. J. M. Sc. **215**: 530–533, 1948.
5. Kierland, R., and Potter, R. T.: An evaluation of thenylene hydrochloride (N,N-Dimethyl-N′-(Alpha-Pyridyl)-N′-(Alpha-Thenyl) ethylenediamine hydrochloride), Am. J. M. Sc. **216**: 20–23, 1948.
6. Beecher, H. K.: Experimental pharmacology and measurement of the subjective response, Science **116**: 157–162, 1952.
7. O'Dea, A. E., and Liss, M.: Suicidal poisoning by methapyrilene hydrochloride with documentation by paper chromatography, New England J. Med. **249**: 566, 1953.
8. Rives, H. F., Ward, B. B., and Hicks, M. L.: A fatal reaction to methapyrilene (thenylene), J. A. M. A. **140**: 1022, 1949.
9. Osgood, E. E.: Report to Council on Pharmacy and Chemistry, Hypoplastic anemias and related syndromes caused by drug idiosyncrasy, J. A. M. A. **152**: 816–818, 1953.

AN EVALUATION OF THE EFFECT OF CHOLINE AND INOSITOL ON THE CLINICAL COURSE AND SERUM LIPIDS IN PATIENTS WITH ANGINA PECTORIS *

By RAYMOND S. JACKSON, M.D., CHAS. F. WILKINSON, JR., M.D., F.A.C.P., LAWRENCE MEYERS, M.D., F.A.C.P., MICHAEL S. BRUNO, M.D., *New York, N. Y.*, and MARTIN R. BENJAMIN, M.D.,† *Stamford, Connecticut*

THE question of whether lipotropic agents might have an effect upon atherosclerosis has been the basis for a number of studies in animals and in man. Clinical investigations have followed along two general lines. Attempts at direct therapeutic evaluation have depended upon the administration of a test substance to patients who have recovered from a myocardial infarction, comparing their course with that of an untreated group of coronary survivors. Strict comparability of methods of managing the basic disease and all concomitant diseases in both the treated and control groups is a necessary part of such a clinical test.

The alternate, more indirect approach has been to administer a test substance to human subjects and to determine whether absolute or relative changes occurred in the various serum lipids during the test period. Such studies are complicated by the spontaneous fluctuations of serum lipids, and by the fact that diarrhea, or anorexia with weight loss, which may result from the treatment, may cause reductions in the serum lipid levels. In an excellent and detailed review of this field Davidson [1] has pointed out the many problems in experimental design which have complicated most of this work.

In this study we have employed both the direct and the indirect approaches. However, we have chosen to use angina pectoris, rather than myocardial infarction, as the disease state to be tested.

The syndrome of angina pectoris is predominantly the result of coronary atherosclerosis.[2] As a test situation, it suffers from the defect of being difficult to prove objectively, but the clinical picture is quite definite in the majority of cases. Its advantage as a test situation lies in the pain produced by the myocardial ischemia, which can be relieved by nitroglycerin. Other things being equal, the amount of pain experienced by the patient

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 8, 1954.

From the Department of Medicine, Post Graduate Medical School, New York University, and the Fourth Medical (N.Y.U.) Division, Bellevue Hospital, New York.

Funds for this study were furnished in part by the Wyeth Laboratories and the Lillia Babbit Hyde Foundation.

† Lillia Babbit Hyde Research Fellow.

The Wychol and the placebo were furnished by the Wyeth Laboratories.

will tend to reflect the degree of coronary insufficiency, and the number of nitroglycerin tablets taken will fluctuate with the amount of pain experienced.

The report cards used in this study (figure 1) were devised to secure this type of information. They are a modification of the cards proposed by Greiner and his colleagues [3] for studies on angina pectoris. The patient was instructed to make two entries on his card each night before retiring: (1) an estimate of the relative amount of pain experienced that day, and (2) the number of nitroglycerin tablets taken. Each card covered a three week period, which was the usual interval between patient visits.

DAILY REPORT CARD

For Securing Data on Cardiac Pain in Patients with Angina of Effort.

BRING THIS CARD TO CLINIC NEXT VISIT

How much pain in the heart did you have each day?

DAY OF THE WEEK	SAME HEART PAIN AS USUAL	LESS HEART PAIN THAN USUAL * GOOD DAY	MORE HEART PAIN THAN USUAL * BAD DAY	NO HEART PAIN AT ALL	NUMBER OF PAIN TABLETS TAKEN TODAY
Sunday					

Before going to bed, each day, write a mark (X) in the space that describes your heart pain for the entire day.

FIG. 1. This shows the instructions on the report card and a sample day.

Subjects for this study were drawn from patients attending the Fourth (NYU) Cardiac Clinic at Bellevue Hospital. Two of us (L. M. and M. S. B.) selected these subjects on the basis of (1) their agreement with the diagnosis of angina pectoris, and (2) their estimate of the ability of the patients to use the report cards. Very few were excluded on this latter basis. When a patient was accepted he was then sent to another room, where another member of the team explained that he was to be given a medication for his heart trouble the effectiveness of which was unknown but which would not harm him. He was then instructed in the use of the report card and given a supply of medication.

On each revisit to the clinic these patients were seen by one of the selecting physicians, who managed their cardiac problems with the usual measures. Vasodilator drugs other than nitroglycerin were not used. Neither these physicians nor their patients had any knowledge of what preparation was being dispensed during the study. Non-cardiac diseases were managed by conventional measures in the other clinics of Bellevue Hospital. The report card was reviewed with the patient each time to ensure the greatest possible accuracy in its use.

At each visit blood was drawn (heparinized) for determinations of plasma cholesterol (total and free) and lipid phosphorus. Cholesterol was determined by the method of Schoenheimer and Sperry.[4] Lipid phosphorus was determined by the application of the method of Simonsen [5] to an alcohol-ether extract of the plasma. This figure was converted to milligrams of phospholipid by multiplying by a factor of 25.

The preparation used in this study was a syrup containing 3.0 gm. of choline and 0.45 gm. of inositol per 15 c.c. (Wychol). The manufacturer

TABLE 1

	Gm. Choline/day		Gm. Inositol/day	
	Range	Mean	Range	Mean
Group I				
A	4.9–11.7	8.9	0.74–1.76	1.33
B	5.8–12.4	9.0	0.87–1.87	1.34
Group II	6.8–12.7	9.8	1.02–1.91	1.47
All	4.9–12.7	9.1	0.74–1.91	1.37

also provided us with similar bottles of the syrupy vehicle alone. The addition of concentrated hydrochloric acid (25 c.c./L.) resulted in a preparation whose taste was similar to though not absolutely identical with the choline-inositol syrup. These two preparations produced similar degrees of gastrointestinal irritation in the doses employed.

A randomized series was followed in starting these patients on either the choline-inositol syrup or the placebo syrup. After six months on the first preparation they were given a three week supply of a mixture of the two in order to minimize the taste difference. Then they were given the second preparation for six more months. Each subject was given a 15 c.c. plastic measuring spoon and encouraged to take 60 c.c. per day in four divided doses. Where this was not possible, lower dosage to the limit of tolerance was allowed. At each visit we recorded the amount of medication remaining and the new supply given. By keeping a record of the amount of medication dispensed we were able to estimate the actual intake of these patients (table 1). Duration of drug treatment is presented in table 2. The groupings shown were made for statistical purposes.

TABLE 2

	Weeks of Choline-Inositol Therapy	
	Range	Mean
Group I		
A	21–29	25.6
B	25–38	28.5
Group II	9–30	23.2

Sixty-three patients were started on this project. Twenty-three are not included in our final data. These failed to complete at least four months of treatment on either the drug or the placebo. Because not all of the remaining 40 had perfectly matched régimes on both drug and placebo, they were broken down into the groups shown in table 4. Group I was comprised of those patients who had had at least four months of treatment

TABLE 3

	Total	Started on	
		Drug	Placebo
Completed Two Periods	27	16	11
Incomplete Experiments			
Medication unacceptable	9 (8)	5 (4)	4 (4)
Lost to project	9 (8)	4 (3)	5 (5)
Project closed	8 (0)	4 (0)	4 (0)
No longer ambulatory	2 (2)	0 (0)	2 (2)
Deaths	3 (1)	1 (0)	2 (1)
Uncoöperative	4 (4)	2 (2)	2 (2)
Moved away	1 (0)	0 (0)	1 (0)
	63	32	31

Figures in parentheses indicate subjects not included in the final analysis.

on both drug and placebo. Group II included those subjects who had taken either the drug or the placebo for at least four months.

Table 3 shows the patterns of treatment for the entire study, and the reasons for failure in the incomplete experiments. "Medication unacceptable" includes those patients who frankly refused for this reason, plus those patients who failed to return to the clinic but who are recorded as having been seen in other clinics at Bellevue following their last project visit. "Lost to project" includes those patients who failed to return as directed

TABLE 4

Group I	
A. Main Analysis	8 placebo-drug sequence 8 drug-placebo sequence
B. Supplementary Analysis	3 placebo-drug sequence 8 drug-placebo sequence
Group II	6 subjects on placebo 7 subjects on drug

and did not answer letters requesting their return. These subjects were not subsequently treated anywhere in Bellevue Hospital, and there is no record of their death in New York City for a period of at least six months following their last visit to the project. It is probable that most of these represent rejections of the medication. The "project closed" patients were those who started late in the course of this study and had not completed the full period when the project was ended. "No longer ambulatory" patients were placed on restricted activity for other than cardiac reasons.

Table 5 summarizes the clinical characteristics of the 40 subjects upon whom we are reporting. Those patients classed as hypertensive had a persistent diastolic blood pressure of 100 mm. Hg or greater. There was no evidence of either cardiovascular syphilis or rheumatic valvular disease

TABLE 5

Sex

Male —33
Female— 7

Age—Mean and Range

Male —62.9 (50–73) years
Female—65.7 (57–74) years
Group —63.4 (50–74) years

Duration of Anginal Symptoms

1 month–16 years. Mean, 4 years.

Etiology

Arteriosclerotic—19
Hypertensive —21

Functional Classification

Class II —20
Class III—20

Therapeutic Classification

Class B— 3
Class C—33
Class D— 4

in any of these patients. Five had electrocardiographic evidence of a previous myocardial infarction, and three of these suffered another infarction during the study. Two others had fresh infarctions during the study without electrocardiographic evidence of a previous episode. One patient had left bundle branch block, another right bundle branch block.

Treatment was interrupted in eight of these patients for cardiac reasons. Table 6 shows the reasons for these interruptions and the treatment the patient had received prior to the interruption. Six out of the eight were on placebo at the time. However, two of these had had prolonged drug treatment previously, and two others had their cardiac episodes after seven months and four months on the drug. The numbers involved here are too small to be conclusive.

TABLE 6

Cardiac Interruptions

	Previous Infarction	Reason for Interruption	Previous Treatment, Months	
			Placebo	Drug
Group I A				
HM	−	CHF	1*	0
Group I B				
HG	+	FMI	1*	0
GH	−	FMI	2*	0
MR	+	CI	2*	8
EB	−	CI	3*	0
Group II				
JB	+	FMI	0	7*
JK	+	FMI	6	4*
MS	−	FMI	1*	6

CHF—Congestive heart failure. FMI—Fresh myocardial infarction.
CI—Coronary insufficiency without infarction.
* Medication being taken at time of interruption.

Non-cardiac interruptions occurred in eight of these patients, as shown in table 7. Except for two who volunteered for another study requiring hospitalization (GH and NP), these represent a variety of non-cardiac illnesses which prevented normal activity. Whenever possible, treatment was resumed after the patient was once more ambulatory.

ANALYSIS OF REPORT CARD DATA

The data collected in this experiment were submitted to Dr. Donald Mainland, of the Department of Biostatistics, College of Medicine, New York University, for an independent analysis.

TABLE 7

Non-Cardiac Interruptions of Treatment

	Previous Treatment—Months	
	Drug	Placebo
Group I A		
MH	0	2*
	0	3*
	1*	6
	4*	6
Group I B		
VA	1*	0
JC	6*	0
GH	1*	6
AH	1*	0
NP	7	1*
EB	0	6*
Group II		
HN	0	6*

* Medication being taken at time of interruption.

To permit a more critical analysis, Group I was separated into two subgroups, A and B (table 4). Four subjects with cardiac interruptions were excluded from the main analysis (Group I A). H. M., who had an episode of congestive failure early in his course (table 5), was included in this group by starting his period of observation after he returned to the project. Of the 23 "non-cardiac interruption" patients in Group I, 15 had been treated in the drug-placebo sequence, eight in the placebo-drug sequence. Because the full analysis requires an equal number in each sequence, eight of the drug-placebo group were selected in such a way as to include as many subjects as possible with an uneventful, uninterrupted

TABLE 8

"Good Days" per 21 Days

	Drug	Placebo	p
Group I A	14.5	12.9	.05
I B	13.1	10.5	.1
II	11.1	11.0	.1

record. The remaining drug-placebo patients and the four "cardiac interruption" patients were put in Group I B.

The report cards were summarized by computing the mean number of "good days" per 21 day period. A "good day" was defined as one for which the subject reported "less pain than usual" or "no pain." Table 8 shows the results of this analysis for each group.

For the patients in Group I A the average number of "good days" per 21 was found to be 14.5 days for the drug, 12.9 days for the placebo. Analysis of variance by the F-test showed that the likelihood of this difference appearing by chance was more than one in 50. We do not consider this a statistically significant difference. Furthermore, the mean difference

TABLE 9

Nitroglycerin Tablets per 21 Days

	Drug	Placebo	p
Group I A	21.9	34.6	.05
I B	22.1	26.4	.1
II	37.1	35.4	.1

of 1.6 "good days" per 21 in favor of the drug seems of dubious clinical significance.

The same type of analysis was carried out for Group I B. The mean number of "good days" per 21 was 2.6 in favor of the drug. This is not a statistically significant difference, though the same trend is exhibited as in Group I A. Group II shows the same pattern, but again the difference is not significant.

The number of nitroglycerin tablets taken per 21 day period was used as another basic measure for comparison purposes (table 9). For Group I A the mean intake of nitroglycerin tablets was 21.9 tablets per 21 days in

the choline-inositol period, and 34.6 tablets per 21 days in the placebo period. The statistical probability of this difference being due to chance is again more than one in 50. Though this reinforces the result of the "days" analysis, again neither the degree of statistical probability nor the absolute magnitude of the difference (12.7 tablets per 21 days) is sufficient to permit a firm conclusion in favor of the choline-inositol therapy.

Group I B again shows the same trend as I A, but the difference is not significant. Those patients in Group II who took the drug averaged 1.7

TABLE 10

Patient-Months on Choline-Inositol and on Placebo Versus Time of Year

	April through September		October through March	
	Drug	Placebo	Drug	Placebo
Group I A	36	54	56	50
I B	30	32	40	32
II	4	3	5	5

more tablets of nitroglycerin per 21 days than did those taking the placebo, a difference which is not significant.

We have looked into possible biases which might explain these differences between drug and placebo in this group of patients. It was found that there was no apparent association between the patient's difference in reaction to drug and placebo and the relative length of time on each treatment. As for the possibility that the drug might have been administered predominantly in the milder months of the year, table 10 shows the pattern

TABLE 11

Patient-Months of Treatment

	April through September	October through March
Group I A		
First Period		
First Half	24	24
Second Half	41	10
Second Period		
First Half	16	34
Second Half	8	37

of patient months as it occurred in this study. The climatic bias seems to be against the drug rather than in its favor.

Tests for trends were carried out using Group I A. These patients showed no evidence that it made any difference whether drug or placebo was administered first. Neither was there any indication of an over-all time trend in the condition of the patients. There was likewise no suggestion of a trend effect with the drug, which was tested for by contrasting

TABLE 12

	Drug	Placebo	p
Group I A			
Mean TC	236.6	216.6	.001
Mean PL	259.2	233.8	.01
Mean PL/FC	4.06	3.93	.2
Group I B			
Mean TC	267.2	242.6	.05
Mean PL	283.7	254.6	.02
Mean PL/FC	3.96	3.91	.1
Group II			
Mean TC	249.6	232.1	.1
Mean PL	264.3	249.9	.1
Mean PL/FC	3.80	3.91	.1

TC—Plasma total cholesterol, mg./100 c.c.
PL—Plasma phospholipid, mg./100 c.c.
PL/FC—Ratio, plasma phospholipid/free cholesterol.

the first half of the period on the drug with its second half. It was found, however, that regardless of the preparation used, these patients tended to improve during the second half of the first treatment period, and to worsen during the second half of the second treatment. This is a peculiar trend effect, upon whose meaning one can only speculate. It does not affect the validity of the drug and placebo comparison. In the nitroglycerin analysis this time trend was not significant ($p > .05$), although the data arrange themselves in the same direction.

One possible factor in this time trend is illustrated in table 11. The patient months of treatment in Group I A are separated into two categories: (a) the milder months of the year, and (b) the more inclement months. As shown, the improvement in the second half of the first period could have been the result of the predominance of the milder patient months in this period, as compared with the pattern of the first half. The worsening of these patients in the second half of the second period is less clearly associated with a climatic bias, though there is a relatively greater preponderance of inclement months during the second half of this period as compared with the first half.

TABLE 13

	First Treatment	Second Treatment	p
Group I A			
Mean TC	230.1	223.1	.05
Mean PL	263.9	229.1	.01
Mean PL/FC	4.27	3.71	.001

TC—Plasma total cholesterol, mg./100 c.c.
PL—Plasma phospholipid, mg./100 c.c.
PL/FC—Ratio, plasma phospholipid/free cholesterol.

Analysis of Plasma Lipid Data

The mean levels of total cholesterol and phospholipid, and the mean phospholipid-free cholesterol ratios,[6] were determined for each patient while on any one treatment. The mean values were then subjected to an analysis of variance in the same manner as were the report card data.

Table 12 shows that the total cholesterol and phospholipid values for Group I A were significantly higher on the drug than on the placebo. Though the same general pattern is seen in Groups I B and II, the differences were not significant except for the phospholipid levels in Group I B. This apparent support of the Group I A findings by Group I B is weakened by the fact that there was a time trend evident in Group I A which presumably would also apply to I B. As shown in table 13, the levels of phospholipid were significantly higher during the first period of treatment than during the second. This finding does not affect the validity of the drug-placebo comparison in Group I A, because an equal number of subjects

Table 14

	Placebo-Drug Sequence	Drug-Placebo Sequence	p
Group I A			
Mean TC	239.8	213.5	.05
Mean PL	248.4	244.6	.05
Mean PL/FC	3.78	4.21	.02

TC—Plasma total cholesterol, mg./100 c.c.
PL—Plasma phospholipid, mg./100 c.c.
PL/FC—Ratio, plasma phospholipid/free cholesterol.

received the drug as first treatment and as second treatment. In Group I B, however, where the majority of patients started with the drug, this time trend necessarily would affect the validity of the drug-placebo comparison.

The phospholipid-free cholesterol ratios showed no significant differences in the drug-placebo comparisons (table 12). However, there was a significant difference in this ratio between the first and second periods of treatment (table 13). Furthermore, when Group I A was analyzed on the basis of sequence (drug-placebo versus placebo-drug), a sequential difference is found for the first time. As shown in table 14, the mean phospholipid-cholesterol ratio was lower in the placebo-drug sequence. We feel that this statistical finding is simply consonant with the general relationship between phospholipid and cholesterol,[6] being what one would expect with the higher cholesterol values in the placebo-drug sequence patients.

The possibility that alterations in general nutrition might have played a part in the differences in the lipids noted between drug and placebo periods has been investigated. These patients were weighed at each clinic visit, but our records are unfortunately not complete in this respect. We were able to determine the weights at the beginning and end of each treatment

TABLE 15

	No. Subjects	Drug Period	No. Subjects	Placebo Period
Group I A				
Mean Initial Weight	12	151.0	12	149.3
Mean Final Weight	12	151.3	12	148.3
Mean Period Weight	9	151.7	9	148.7
Group I B				
Mean Initial Weight	9	143.9	9	144.7
Mean Final Weight	9	143.3	9	143.3
Mean Period Weight	2	122.3	2	116.8
Group II				
Mean Initial Weight	4	135.8	5	143.6
Mean Final Weight	4	136.3	5	144.8
Mean Period Weight	3	135.4	5	144.8

period in the majority. Weights of sufficient frequency (80% of visits) to allow calculation of mean weights for each treatment period were available for about half of these patients. Table 15 shows that the mean weights tended to be slightly lower during the placebo periods in Group I, but these patients began and ended each period at about the same weights. Reasonably close approximation of beginning and ending weights for both first and second treatment periods are demonstrated in table 16. It seems unlikely, therefore, that weight changes can account for the differences noted in the plasma lipids between drug and placebo periods and between first and second treatments.

Though the higher lipid levels observed during drug treatment in Group I A are statistically valid, the similar findings when first and second treatments are compared raise the question of the operation of a common denominator between "first treatment" and "drug period" in these patients. A factor which must be considered is the seasonal pattern of these two periods. Tables 10 and 11 show that while the inclement months predominate in the "drug periods," the milder months predominate in the "first treatments."

Finally, a within-patient variance analysis was carried out in Group I A by a method analogous to that used for the analysis of the means. There

TABLE 16

	No. Subjects	First Treatment	No. Subjects	Second Treatment
Group I A				
Mean Initial Weight	12	150.3	12	149.9
Mean Final Weight	12	149.7	12	150.0
Mean Period Weight	9	150.8	9	149.6
Group I B				
Mean Initial Weight	9	145.1	9	143.4
Mean Final Weight	9	143.4	9	143.2
Mean Period Weight	2	122.3	2	116.9

was no evidence that administration of the drug affected the fluctuations of total cholesterol or of phospholipid in these patients, as compared with their fluctuations while on the placebo.

Summary

1. Forty patients with angina pectoris were studied in a double-blind experiment to test the effect of a choline-inositol syrup on their symptoms and on the levels of their plasma lipids.

2. No statistically significant symptomatic improvement could be demonstrated.

3. The mean levels of plasma cholesterol and phospholipid were significantly higher during choline-inositol therapy.

4. Fluctuations of plasma cholesterol and phospholipid were not significantly affected by the choline-inositol treatment.

BIBLIOGRAPHY

1. Davidson, J. D.: Diet and lipotropic agents in arteriosclerosis, Am. J. Med. **11**: 736, 1951.
2. Zoll, P. M., Wessler, S., and Blumgart, H. L.: Angina pectoris. A clinical and pathologic correlation, Am. J. Med. **11**: 331, 1951.
3. Greiner, T., Gold, H., McKeen, K., Travell, J., Bakst, H., Rinzler, S. H., Benjamin, Z. H., Warshaw, L. J., Bobb, A. L., Kwitt, N. I., Modell, W., Rothendler, H. H., Messeloff, C. R., and Kramer, M. L.: A method for the evaluation of the effects of drugs on cardiac pain in patients with angina of effort, Am. J. Med. **9**: 143, 1950.
4. Sperry, W. M.: The Schoenheimer-Sperry method for determination of cholesterol, Rev. Ed., 1945, Department of Biochemistry, Psychiatric Institute, New York.
5. Simonsen, D. G., Wertman, M., Westover, L. M., and Mehl, J. W.: The determination of serum phosphate by the molybdivanadate method, J. Biol. Chem. **166**: 747, 1946.
6. Jackson, R. S., and Wilkinson, C. F., Jr.: The ratio between phospholipid and the cholesterols in plasma as an index of human atherosclerosis, Ann. Int. Med. **37**: 1162, 1952.

THE EFFECT OF LEVO-THYROXINE, DEXTRO-THYROXINE AND LEVO-TRI-IODO-THYRONINE ON THE ELECTROCARDIOGRAM IN MYXEDEMA: PRELIMINARY REPORT *†

By PAUL STARR, M.D., F.A.C.P., and RUTH LIEBHOLD-SCHUECK,
Los Angeles, California

THIS preliminary report concerns the beginning of a study of the action of thyroxine on the heart. Its effects are so powerful and beneficial in the case of the heart of the hypothyroid patient that its therapeutic value in other kinds of heart disease should be determined. This will require a careful analysis of the pharmacology of thyroxine, to which these observations are a brief introduction. This seems to be the obverse of the therapeutic induction of hypothyroidism in heart disease that is now being advised.

Death during the first few days of the treatment of myxedema with desiccated thyroid has been reported in the past.[1] It constitutes the basis for the knowledge that overtreatment may be dangerous. Angina pectoris during the rejuvenation of the myxedema patient by the thyroid hormone is a common occurrence; it is observed before the metabolic load is greatly increased, and indicates a pharmacodynamic action of thyroxine on the heart.

Thyroid hormone, excessive, normal or insufficient, may be supposed to affect the heart by each of three mechanisms: (1) pharmacodynamic, (2) metabolic, and (3) histologic.

1. The pharmacodynamic effect of the thyroid hormone on the heart was first indicated by Asher in 1911,[2] and was corroborated by Lewis in 1931.[3] This effect may be stated as follows: The hyperthyroid heart is more sensitive to epinephrine than the normal heart; conversely, the hypothyroid heart is less sensitive.[4] Hence, the heart in myxedema is receiving subnormal adrenergic myocardial action. As a result, the early electrocardiographic changes in myxedema under treatment may be due to adrenergic substances which appear before thyroxine effects in the rest of the body are evident.

Brewster, Isaacs and Osgood [5] have just extended, and repeated in dogs made hyperthyroid by thyroid feeding, the fundamental thesis of Asher, i.e., they report "consistently greater increases in oxygen consumption, cardiac rate and cardiac index with infusion of epinephrine or nor-epinephrine in the thyrotoxic dogs than occurred with the same infusion in euthyroid

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 9, 1954.

† Supported in part by Baxter Laboratories, Morton Grove, Illinois, U. S. Public Health Service (Grant No. C-1214(C3)), and Smith, Kline and French Foundation.

From the Thyroid Clinic of the Los Angeles County Hospital and The Department of Medicine of the School of Medicine, University of Southern California.

dogs." They considered "that the cardiovascular *and* calorigenic effects of thyrotoxicosis are not due to a direct effect of thyroxine per se but rather to an augmentation of the physiological effects of epinephrine or norepinephrine by thyroxine."

2. The general increased metabolic rate in hyperthyroidism undoubtedly is associated with greater work of the heart[6]; furthermore, decreased peripheral resistance makes the entire circulation take on the characteristics of an A-V shunt mechanism, which requires increased cardiac output. This may be especially true if a large goiter with enormous blood supply is present to provide a localized A-V shunt.

3. The morphologic changes in the myocardium in myxedema are well known; those resulting from hyperthyroidism have not been described. The myxedematous heart is enlarged; the myocardium is reddish brown in color, very friable, and easily penetrated with the finger. Microscopically, the muscle bundles, muscle fibers and connective tissue are widely separated by interstitial edema.[1] The electrocardiographic phenomena may easily be due to the physical changes induced in the tissues.

Methods

Whenever myxedema was suspected, patients were studied for athyreosis by determination of the serum protein-bound iodine, uptake of radioactive iodine before and after three daily intramuscular injections of TSH (Armour's Thytropar*) and basal metabolic rate. Frequent clinical electrocardiographic and laboratory observations were carried out before and during the oral administration of sodium levo-thyroxine pentahydrate,† sodium dextrothyroxine pentahydrate † and levo-tri-iodo-thyronine.‡ The specific rotations of the thyroxine isomers were equal in magnitude (approximately 6.5°) but opposite in sign, suggesting that each was reasonably free of the other. There is little likelihood that as much as 10% racemization had occurred in either thyroxine.

Clinical Examples

Case 1. Mrs. D. C. was first seen here in July, 1950, with an eight months' history of nervousness and weight loss. Laboratory tests at the time were as follows: I^{131} uptake, 70%; basal metabolic rate, plus 47%; serum protein-bound iodine (PBI) 8.7 μg.%. She was clinically thyrotoxic. A treatment dose of 8 mc. of I^{131} was given and the patient was subsequently discharged from the hospital. She did not return until 11 months later, when she was admitted in a state of fully developed myxedema. Her PBI determinations were between 1.0 and 1.7 μg. per 100 c.c. of serum; cholesterol was up to 360 mg. per 100 c.c. of serum; I^{131} uptake was 1.5% in 24 hours. She was started on thyroid medication three times, but on each occasion

* Provided by the generous coöperation of the Armour Laboratories, Chicago.
† Provided by the generous coöperation of Dr. Leonard Ginger, Baxter Laboratories, Morton Grove, Illinois.
‡ Provided by the generous coöperation of Dr. Arthur Heming, of Smith, Kline and French, Philadelphia.

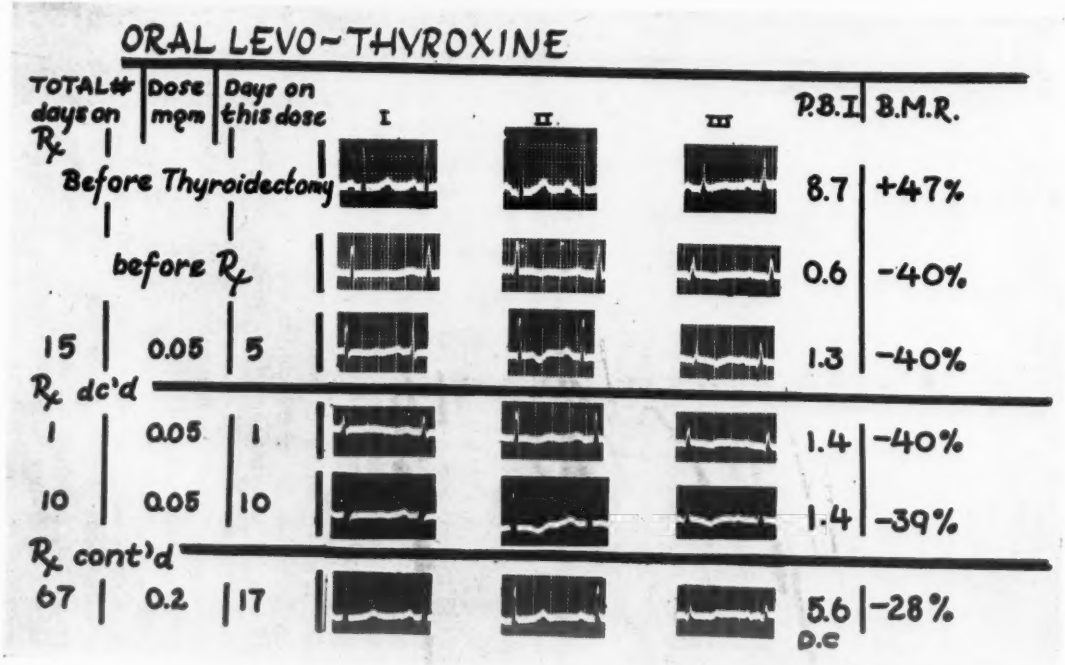

FIG. 1. Case 1. Note first evidence of electrocardiographic effects on fifth day of 0.05 mg. daily oral levo-thyroxine, indicated by inversion of T wave in Lead II. Serum protein-bound iodine at this time, 1.3; basal metabolic rate, minus 40%.

she failed to return for continued treatment, and reappeared when she was fully myxedematous. She was hospitalized again in November, 1953, with a PBI of 0.6, a basal metabolic rate of minus 40%; cholesterol of 535 mg.%. She was started on 0.05 mg. sodium levo-thyroxine daily. About one week after this treatment had been started, T_2 and T_3 in the electrocardiogram (figure 1) became inverted and she developed some ankle edema. At this point her PBI had come up to 2.1% but her basal metabolic rate was still minus 38%. Thyroxine medication was discontinued. The ankle edema promptly disappeared and the T-waves returned to the iso-electric myxedematous level. She was again started on 0.05 mg. sodium levo-thyroxine daily seven days after this same treatment had been interrupted. The T-waves of the electrocardiogram again became inverted, but she did not develop ankle edema. She was carefully observed and kept on this dose for two weeks. This was subsequently increased to 0.1 mg. and 0.2 mg. sodium levo-thyroxine. Her T-waves gradually improved, became upright, and eventually returned to normal.

Her basal metabolic rate is now minus 17%, her serum PBI is over 6 μg.%, and she is clinically much improved.

Discussion: The T wave inversion in Leads II and III was not due to the patient's posture or deep inspiration, for they appeared and remained for several days on each occasion of treatment with 0.05 mg. of sodium levo-thyroxine. They may indicate relative ischemia in the heart muscle, but may be one of the first indications of adrenergic action, either as a coronary artery effect or as a thyroxine effect on the muscle fibers. It seems unlikely that the work load of metabolism was responsible, because the basal metabolic rate was still minus 38% when this first occurred.

Case 2. Mrs. I. L., age 61, had had known spontaneous postmenopausal myxedema for at least 10 years with irregular substitution thyroid therapy. Diagnostic studies indicated that the radioactive iodine uptake was low, 5.3% before and only 7.3% after three daily intramuscular injections of 15 mg. of thyrotropic hormone. Since the amount of functioning thyroid tissue present was negligible, the effects shown in figure 2 may be attributed to daily oral sodium levo-thyroxine.

Discussion: It is to be noted that there is a slight, abrupt, significant effect appearing on the eighth day of medication when the serum protein-bound iodine was 2.3 μg.%. At this time the basal metabolic rate was estimated by interpolation to be minus 35%, i.e., the early electrocardiographic changes appeared at an extremely low circulating thyroid hormone level and at a very low basal metabolic rate. It is interesting that 24 hours before this there was no electrocardiographic evidence of thyroxine activity in the myocardium. Further changes are observed as treatment continues. With a daily dosage three times as great, i.e., 0.3 mg. compared to 0.1 mg., there is no significant change in basal metabolic rate—minus 8% vs. minus 10% —and no significant change in PBI—5.8% vs. 6.9%. In contrast, the electrocardiographic changes are markedly greater on the larger dosage.

Case 2 (continued). Further studies in the case of Mrs. I. L. (case 2) were made with sodium dextro-thyroxine. The high peaked T-waves in her electrocardiogram while on levo-thyroxine continued for 11 months on a daily dosage of 0.3 mg. (figure 3). This was associated with a steady state of basal metabolism (minus 9%)

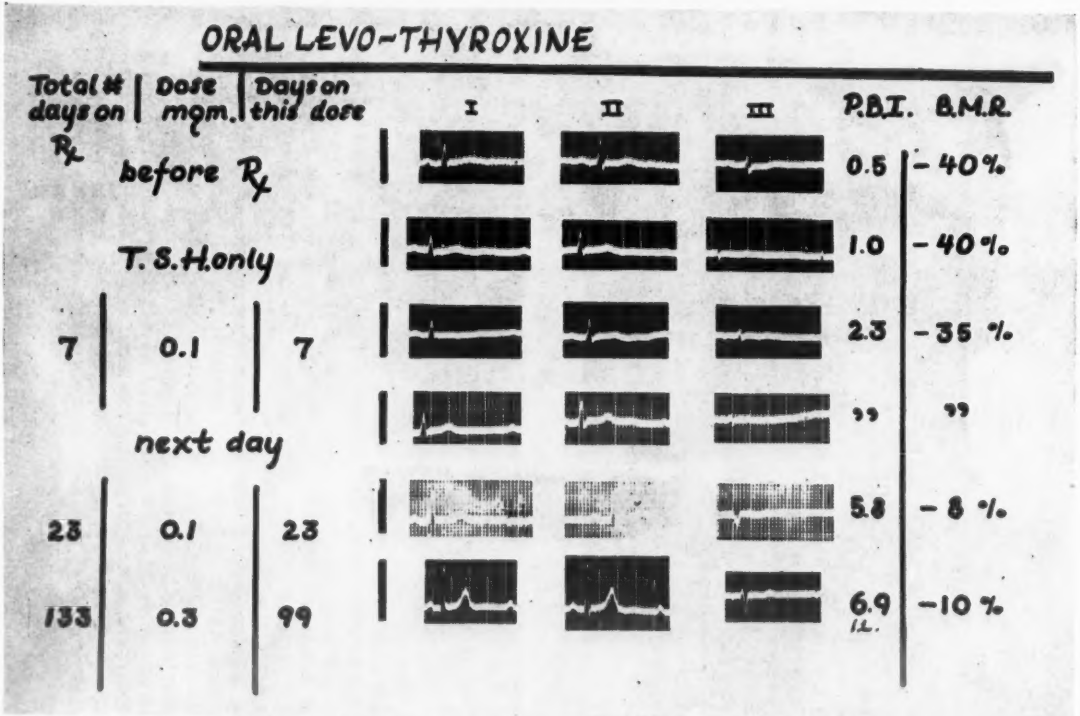

FIG. 2. Case 2. First indication of electrocardiographic changes on eighth day of medication with oral levo-thyroxine, 0.1 mg. daily. Serum protein-bound iodine at this time, 2.3; basal metabolic rate, minus 35%; electrocardiogram on 0.3 mg. corresponds to dosage rather than to metabolic rate.

and PBI 6.5 μg.%. Substitution of 0.3 mg. of sodium dextro-thyroxine was followed by a gradual fall in PBI and basal metabolic rate to a steady state of 2.4 μg.% and minus 26%, respectively. This was coincident with much lower T-waves (figure 3).

Case 3. The administration of sodium dextro-thyroxine, in dosage tenfold that of the customary levo-thyroxine prescription, was studied in the case of Miss R. T., a hypothyroid dwarf 32 years old. She had the mentality and bone age by x-ray of a child of eight. She was untreated. The serum protein-bound iodine was 0.8 μg.%, the blood cholesterol 470 mg.%, and the basal metabolic rate minus 40%; the 24 hour radioactive iodine uptake was 1.7% before and 0.31% after three daily injections of thyrotropic hormone.

She was given 0.5 mg. of sodium dextro-thyroxine daily by mouth. This is 10 times the amount (0.05 mg.) of sodium levo-thyroxine that would have been used. The results are striking (figure 4). Comparison and biochemical study of the two isomers will be reported later. After one month of medication the serum protein-bound iodine was 4.0 μg.%, and the basal metabolic rate was minus 18%. At this time the dosage of sodium dextro-thyroxine was doubled, i.e., 1.0 mg. a day was given. After she had been on this therapy an additional month the serum protein-bound iodine was 7.5 μg.%, and the basal metabolic rate was minus 10%. Electrocardiographic changes are shown in figure 4.

Case 4. Mrs. E. J. entered the hospital because of cardiac decompensation with associated Cheyne-Stokes respiration. Because of her appearance, the presence of myxedema was suspected. A serum PBI was found to be 1.5 μg.% (figure 5). The electrocardiogram was interpreted by Dr. R. C. Lewis as "abnormal EKG. Left ventricular hypertrophy." An attempted basal metabolic rate test was unsatisfactory, but showed dyspnea alternating with apnea. Treatment of cardiac dropsy was followed by a weight loss of 23 pounds (from 147 to 124 pounds).

Because of the possibility that myocardial improvement would occur before the metabolic load was too great, tri-iodo-thyronine was started as an oral medication, given once a day in a dosage that had been found to depress the I^{131} uptake of normal subjects,[7] 8.8 μg. This minute dose had no apparent action. Cautious increases were made from time to time. The effects of this treatment on the electrocardiogram, weight, serum protein-bound iodine and respiration are shown in figure 5. Attention is called to the abrupt change between the sixty-third and seventieth days, when the dosage had been 0.035 mg. for three weeks. Note also that there is no increase in the serum PBI with this medication, and that the Cheyne-Stokes respiration disappears.

Case 5. Mrs. M. K. suffered from spontaneous myxedema. The serum protein-bound iodine was 1.5 μg.%, the basal metabolic rate was minus 40%, the serum cholesterol was 1,070 mg.%, and the radioactive iodine uptake was 9.7% before and 8.3% after three daily intramuscular injections of thyrotropic hormone. She was cautiously started on 8.8 μg. (0.0088 mg.) of tri-iodo-thyronine by mouth once a day. After 43 days the basal metabolic rate was minus 37% and the serum protein-bound iodine 0.8 μg.%. On the forty-third day the daily dosage was increased to 17.5 μg., on the eighty-fourth day to 35 μg.%, and after three and one-half months to 70 μg. a day. With this dosage the basal metabolic rate was normal (minus 9%), but the serum protein-bound iodine was repeatedly less than 1μg.%. The serum cholesterol was still elevated and the blood count was still below normal (hemoglobin, 11.3 gm.; red blood cells, 3,600,000; white blood cells, 4,400). An increase in the eighth month to 105 μg. per day (0.105 mg.) was associated with a serum protein-bound iodine of 0.4 μg.% and a basal metabolic rate of plus 3%. Electrocardiographic changes are shown in figure 6.

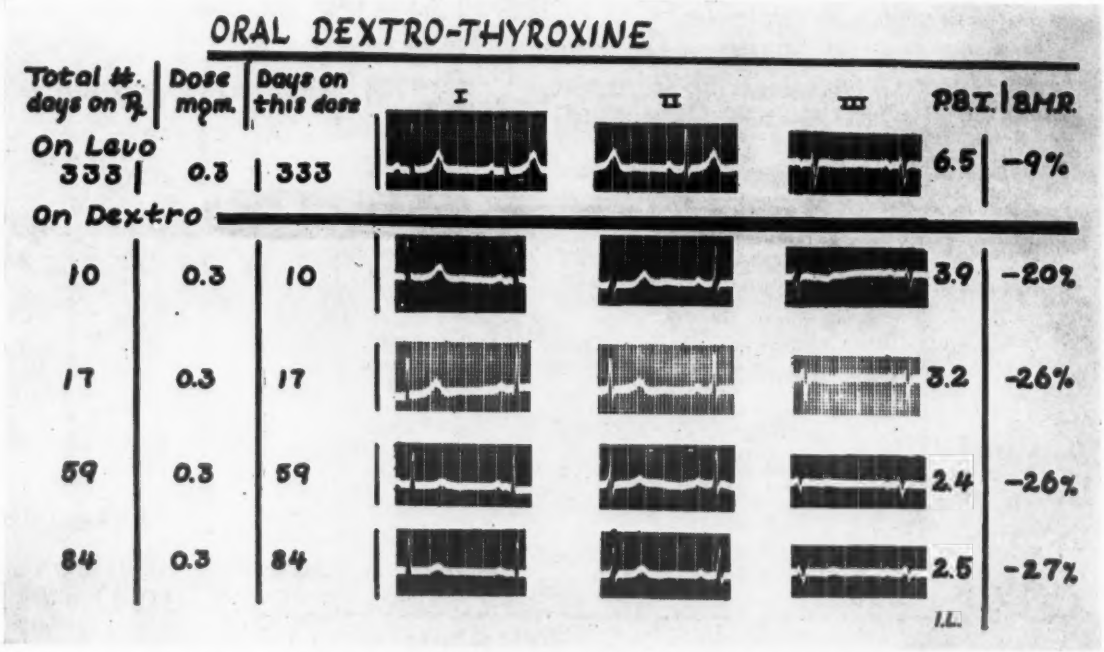

FIG. 3. Case 2 continued. Gradual decrease in electrocardiogram potential and change from 0.03 mg. oral levo-thyroxine to same dose of oral dextro-thyroxine.

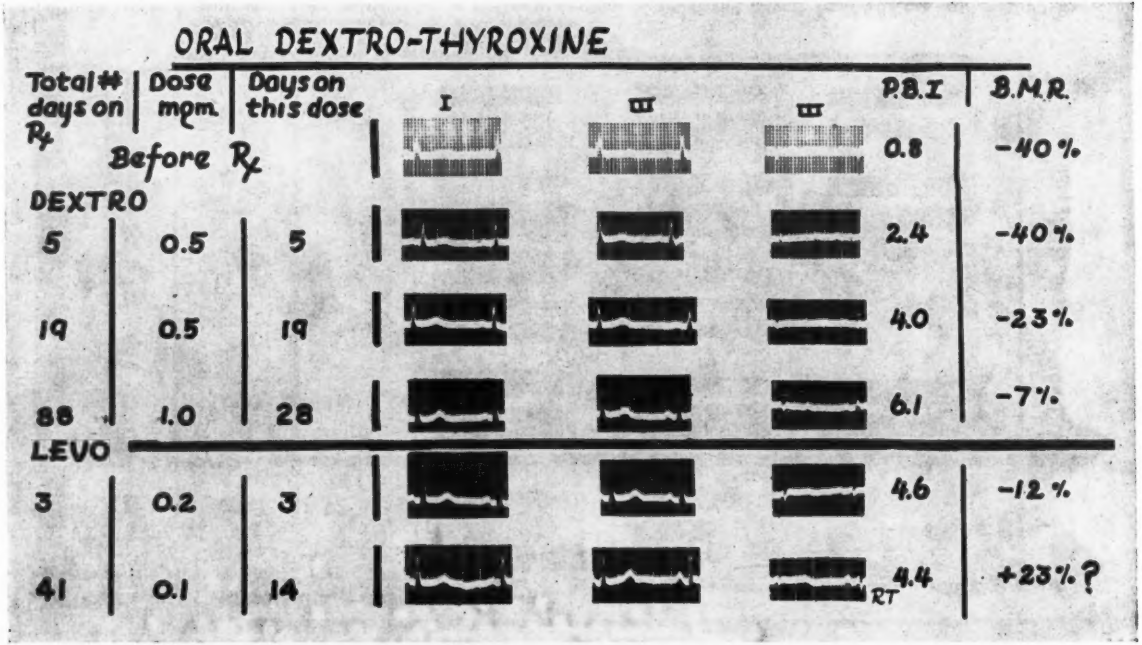

FIG. 4. Electrocardiogram changes on 1 mg. daily oral dextro-thyroxine, as compared to 0.2 mg. daily oral levo-thyroxine.

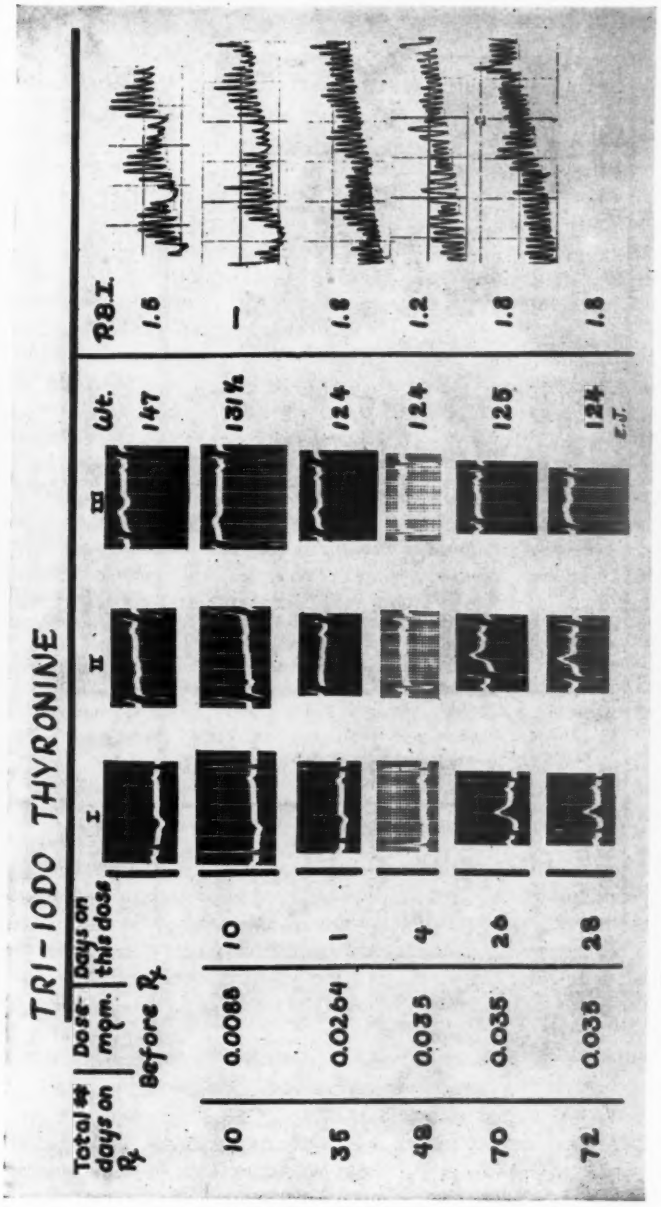

FIG. 5. Normal electrocardiogram potential with serum protein-bound iodine, 1.8 μg. %.

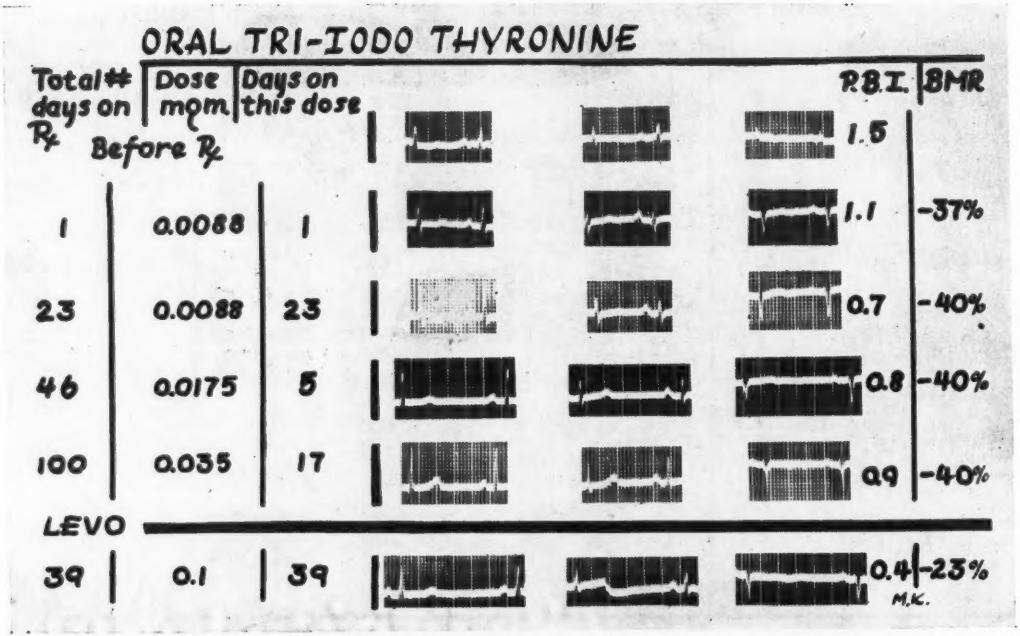

FIG. 6. Significant electrocardiographic changes on oral tri-iodo-thyronine with basal metabolic rate minus 40, and serum protein-bound iodine, 0.9%.

Discussion

In several cases the electrocardiogram began to change toward normal and occasionally became normal before the serum protein-bound iodine or metabolic rate became normal. This was by no means constant, but was so frequent as to suggest that the pharmacodynamic action, i.e., the potentiation of the epinephrine effect on the heart, was occurring before the general elevation of body metabolism was produced by the medication. The usual understanding is that the heart responds to the metabolic demands of the body for more oxygen; these serial measurements suggest that the heart is affected by the thyroid hormone directly, possible via the adrenergic substances, the histochemical or the cellular changes, and is not merely responding to an increased work load.

These observations reëmphasize the classic dictum that the treatment of myxedema begins with a fraction of the final maintenance dose because of danger to the heart. They seem to indicate that the danger lies in the pharmacodynamic action of the thyroxine on the pathologic heart muscle and not in its ability to raise the metabolic rate.

A comparison of the three analogues of the thyroid hormone in these studies—levo-thyroxine, dextro-thyroxine and tri-iodo-thyronine—raises many more questions than are answered. Much to our surprise, dextro-thyroxine had a definite effect on the electrocardiogram, but has had less effect in equal dosage than levo-thyroxine. This might mean that it acted as such, but might also mean that it is converted to the levo form of thyroxine. As was expected, tri-iodo-thyronine seemed to have a more marked effect on the electrocardiogram than levo-thyroxine (see figures 5 and 6). This was associated in case 5 with serum protein-bound iodine values unchanged from those of the pretreatment determinations. Further study of the pharmacodynamic action of thyroxine is indicated.

Summary

The effect of thyroid hormone in myxedema is probably threefold: (1) pharmacodynamic via adrenergic potentiation;[2] (2) indirect, through increased metabolic body demands, and (3) histologic. Levo-thyroxine frequently produces initial electrocardiographic changes before the circulating PBI or basal metabolic rate is normal. It is probable that the electrocardiogram should be used as a guide to dosage rather than the PBI or basal metabolic rate.

Dextro-thyroxine has a definite effect on all these laboratory determinations.

Tri-iodo-thyronine produces similar electrocardiographic effects at very low dosage without any increase in the serum protein-bound iodine, and without elevation of basal metabolic rate.

Six examples, two with each substance, are given. A myxedematous

patient with congestive heart failure and Cheyne-Stokes respiration was successfully treated with tri-iodo-thyronine.

Further study of the pharmacodynamic action of thyroxine on the heart is warranted.

BIBLIOGRAPHY

1. Means, J. H.: The thyroid and its diseases, 2nd Ed., 1948, J. B. Lippincott Co., Philadelphia.
2. Asher, L., and Flach, M.: Beitrage zur Physiol. der Drusen, Ztschr. f. Biol. **55**: 83, 1911.
3. Lewis, J. K., and McEachern, D.: Persistence of accelerated rate in isolated hearts of thyrotoxic rabbits; response to iodides, thyroxine and epinephrine, Bull. Johns Hopkins Hosp. **48**: 228, 1931.
4. Eppinger, H., Falta, W., and Rudinger, C.: Über die Wechselwirkungen der Drüsen mit innerer Sekretion, Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs. **3**: 810, 1908.
5. Brewster, W. R., Jr., Isaacs, J. P., and Osgood, P. F.: Relationship of L-thyroxine to cardiovascular, calorigenic and metabolic effects of L-epinephrine and L-norephinephrine, Federation Proc. **13**: 559 (Mar.) 1954.
6. Stewart, H., Deitrick, J. E., and Crane, N. F.: Studies of the circulation in patients suffering from spontaneous myxedema, J. Clin. Investigation **17**: 238 (May) 1938.
7. Starr, P., and Liebhold-Schueck, R.: Effect of oral thyroxine and tri-iodo-thyronine on radioactive iodine uptake and serum protein bound iodine in normal human subjects, Proc. Soc. Exper. Biol. and Med. **83**: 52–54, 1953.

ON SOME FEATURES OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE AS SEEN IN THE NATIONAL CARDIOLOGICAL INSTITUTE OF MEXICO *

By M. Salazar-Mallén, F.A.C.P., and José Rulfo,
Mexico, D. F.

Mexico constitutes a rich field for the study of variables, such as the influence of genetic (racial) constitution and climate upon the development of many socially important diseases. The country is populated by representatives of isolates that can be considered as racially unmixed (pure) Indians, as well as by whites (mainly from Spain) and, what is ethnologically predominant, a mixture of both. At the same time, in its large area Mexico has desert lands, snow-capped mountains, temperate valleys and tropical areas. Geopathology thus deserves a unique place as a part of our national pathology.

Since the fundamental report by Chavez [1] it is known that rheumatic heart disease plays an outstanding rôle as a cause of cardiopathy in Mexico. As a matter of fact, the country has in this respect a position not unlike that of countries where rheumatic fever and its sequelae are considered a public menace. The rheumatic state seems to develop according to some genetic traits, and also to follow a pattern in its morbidity that can be correlated with climatic conditions. In order to acquire an insight into the influence of our racial traits, climate and other etiologically important factors we have analyzed in this study the data provided by consultations in the National Cardiological Institute from 1944 to 1950.

Definition

In this paper we will consider as rheumatics only cases of rheumatic fever and rheumatic heart disease. The same connotation in respect to etiology will be given the cases that our records include as pericarditis, myocarditis, endocarditis and rheumatic pancarditis.

Material of Study

Our data take into consideration clinical records kept at the Institute from 1944 to 1950. In 1951 the Institute was enlarged and remodeled and the number of cardiac consultations was restricted. The entries for 1952 have been only partially classified.

* Received for publication June 7, 1954.
From the Immunology Laboratory and the Department of Biostatistics, National Cardiological Institute, Mexico.

To establish the majority of our figures and indices we resorted to the use of data obtained through the mechanical tabulation of perforated cards. However, in some instances it was necessary to check the clinical records individually; for example to obtain data concerning the rheumatic onset, we examined 1,200 records, obtaining the necessary information from 451.

Results

A. *Relative Frequency of Rheumatism in the Mexican Republic:* During the six years studied, 26,091 patients were admitted to the Institute. Of these, 5,531 were rheumatics, and 11,012 cardiacs without rheumatism (including those with vascular diseases). Hence the rheumatic/total cardiac index (r/t) can be figured at 0.3343.

In table 1 the values obtained by us are compared with data from Professor Ignacio Chavez and other Latin American investigators.

Table 1

Relative Frequency of Rheumatic Heart Disease in Various Latin American Countries

Chávez[1] (Mexico)	Salazar M. (Mexico)	Celis[2] (Lima)	Cossio[3] (Argentina)	Morais[4] (Recife)	Osorio[5] (Río Grande)	Suárez[6] (Puerto Rico)	Tranchesi[7] (Sao Paulo)
0.4108	0.3343	0.0987	0.1790	0.1532	0.1240	0.1731	0.1731

B. *Frequency According to Sex:* Of the total rheumatics (5,531), 65.27% were females. The predominance of the female sex, when compared with that seen in other forms of cardiopaths, is statistically very significant (p. less than $1 \times 400{,}000{,}000{,}000$).*

C. *Frequency According to Age:* This subject can be subdivided as follows:

1. The age of the patients at the time of their consultation at the Institute: average of the 5,531 patients: 26.83 years, S. D. 14.18, with extremes of one year and 84 years of age.

2. Age when the rheumatism first attacked: referring to cases diagnosed as rheumatic fever (without fundamental heart attack), the average, obtained from 124 records, was 14.75 years, S. D. 10.13; furthermore, in 69.35% of the cases the disease started before 21 years of age; in 91.93% before 31 years, and in 46.49% between 10 and 15 years. The extremes are one year and 55 years of age.

3. Age of rheumatic cardiopathy onset: in the 327 records herein classified as cases of rheumatic heart disease (endomyocarditis), the age of onset was 17.55 years, S. D. 10.72, with extremes of two and 59 years.

The difference between the average ages of the second and third groups is not statistically significant at the 5% level.

* In the population of cardiopaths without rheumatism, which was used as a comparison (9,054 cases), the proportions are 42.27% men and 57.73% women.

D. *Geographic Distribution of Rheumatism in the Mexican Republic:* This is a matter of great importance because of the relation between morbidity and climate, as well as its possible relation to other factors which may cause confusion in the opinions concerning the hereditary hypothesis of rheumatism, as sustained by Wilson [8] and ourselves.[9]

When referring to the general frequency of rheumatism we use the index (r/t) of relative morbidity. This figure is, as mentioned before, 33.43 (0.3343) for the whole cardiac population studied in our Institute. The following list has been compiled for the different States of the Republic:

TABLE 2

Rheumatic Index, Geography and Climate

Name of State	Index r/t	Number of Cases	Predominant Climate[10]
State of Mexico	0.6521	380	Temperate-rainy
Puebla	0.6260	200	Temperate-rainy
Tlaxcala	0.6000	88	Temperate-rainy
Federal District	0.5990	13,426	Temperate-rainy
Guanajuato	0.5843	263	Temperate-rainy
Hidalgo	0.5714	220	Temperate-rainy
Michoacan	0.5536	362	Temperate-rainy (tropical)
Guerrero	0.5000	111	Tropical-temperate-rainy
Jalisco	0.4019	143	Tropical-temperate-rainy
Nuevo Leon	0.3333	32	Dry
Morelos	0.3253	110	Temperate-tropical-rainy
Zacatecas	0.3125	63	Dry
Chihuahua	0.3043	60	Dry
Aguascalientes	0.3043	30	Dry-temperate-rainy
Oaxaca	0.2958	92	Tropical-rainy-dry
Queretaro	0.2833	77	Dry-temperate-rainy
San Luis Potosi	0.2456	71	Dry
Veracruz	0.2396	238	Tropical-rainy
Durango	0.1951	49	Dry
Colima	0.1875	19	Tropical-rainy
Yucatan	0.1612	36	Tropical-rainy-dry
Sinaloa	0.1500	46	Tropical-rainy-dry
Coahuila	0.1428	96	Dry
Tamaulipas	0.1142	78	Tropical-rainy
Tabasco	0.0967	34	Tropical-rainy
Chiapas	0.0845	77	Tropical-rainy
Sonora	0.0810	40	Dry
Nayarit	0.0606	34	Tropical-rainy
Campeche	9 cardiacs, without rheumatism		Tropical-rainy

Table 2 shows the variability of our index of rheumatic morbidity according to the climate. The States and Territories of Baja California, Campeche and Quintana Roo were eliminated from the list because of the scarcity of data obtained from them. Initial attacks of rheumatism were not recorded in some States where the predominant climate is tropical-rainy and tropical-dry (Chiapas, Tabasco and Yucatan). Case records of the onset of rheumatism in Veracruz (predominant climate: tropical-rainy), Durango and Chihuahua (dry climate) were found, but most of the initial attacks were registered from states with a predominantly temperate climate (Mexico, Mexico City, Puebla, Hidalgo, et cetera).

E. *Seasonal Character of Rheumatism:* From 708 records of rheumatic patients, dates pertinent to the seasonal activity of rheumatism were obtained in 79. In figure 1 the annual distribution of the rheumatic attacks is presented. It will be noted that, according to our data, the majority of the initial attacks took place during the middle and end of summer (August-September) and the end of spring (April-May). The minimum incidence corresponds to the winter months.

F. *Economic-Social Classification and Rheumatism:* The Social Service Department of the Institute classifies the financial status of every patient

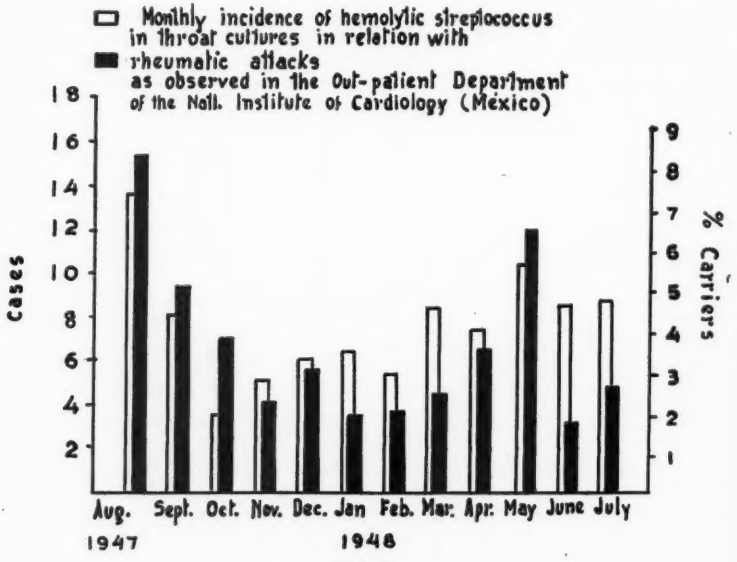

FIG. 1.

receiving clinical services. The rheumatic morbidity indices corresponding to the different economic classes are shown in table 3.

It will be noted that the index gradually decreases as the income increases. The difference between the classes A and F is statistically very significant (X^2 6.79 for 1 D. F.); the comparison between the A and D groups (X^2 equals 3.56) is also significant. On the other hand, one is impressed by the proportions of rheumatics in the different classes: 82.34% are classified as individuals with very low incomes or in very poor economic (financial) conditions. Our studies can be compared with the results obtained by Professor Chavez, who found a higher proportion of rheumatics in hospital charity patients than in his private practice.

G. *Observations Regarding the Frequency of Rheumatism since 1944 (Using the r/t Index as a Starting Point):* According to some investigators,

TABLE 3

Economic-Social Classification and Rheumatism

Class	Definition	Total Number		
		Cardiacs	Rheumatics	r/t Index
A	Indigent	2,673	1,102	0.412
B	Very low income	6,168	2,481	0.402
C, D	Low income	964	317	0.328
E	Moderate income	928	353	0.380
F	Rich	312	98	0.314

The difference between A and D is statistically significant at the 5% level.

a decrease of rheumatism can be assumed in the whole world during the past years. Our rheumatic index values (r/t) are as follows: in 1944, 0.3974; in 1946, 0.2899; in 1947, 0.3742; in 1948, 0.3501; in 1949, 0.3264; in 1950, 0.2201 (figure 2). The values vary considerably each year. It is, however, interesting to note that there has been a large increase in the number of cardiac consultations in comparison with those of rheumatics. The values for the former are 1687, 1704, 2020 and 2613, and for the latter, 689, 929, 918, 979 and 781 (from 1946 to 1950).

IV. DISCUSSION

Our data plainly demonstrate the prominent rôle which rheumatism as a cause of heart disease plays in Mexico. Our index is lower than the one

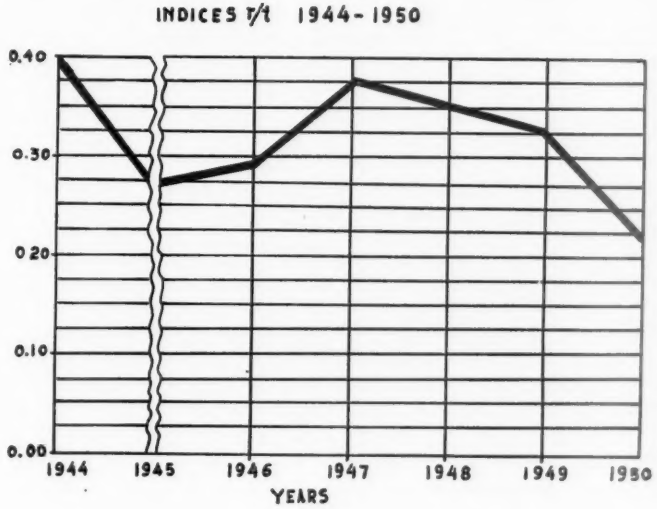

FIG. 2.

given by Professor Chavez in 1942. (It should be specified that he did not include thyrotoxicosis cases in his denominator, whereas we did.) On the other hand, our value is higher than that obtained in other Latin American countries which, considering the racial mixture of our population, shows the lack of immunity of the Indian component of our genotype to the rheumatic agent. As a matter of fact, rheumatism occupies just as important a place in Mexico as in Anglo-Saxon countries, where it is considered a real menace from the social point of view.

The predominance of the female sex in the rheumatic population, as demonstrated by other investigators, and especially by Professor Chavez (whose figure of 59% is lower than ours, 65.27%), makes it imperative to discuss the mechanism of the hereditary rheumatic predisposition, sustained

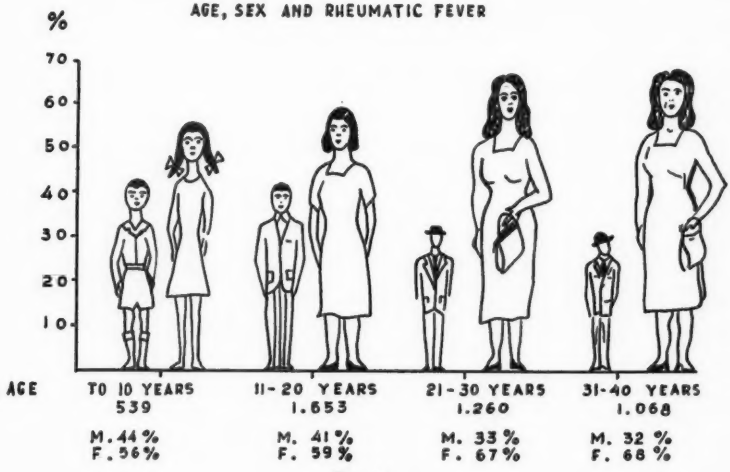

FIG. 3.

in previous publications by Wilson and by ourselves. According to this hypothesis of transmission by a pair of autosomic recessive factors, no difference should be noted between the proportions of rheumatism in the two sexes. Notwithstanding, our data can be interpreted without the intervention of factors located in the X chromosome, as the unfavorable balance for women occurs mainly during the reproductive period (figure 3).

The noticeable feminine predisposition to allergy in general and to certain hyperergic reactions (lupus erythematosus, erythema induratum) is well known (Bray), and Gold [11] interprets it as due to "the instability of the pituitary-adrenal system during the female genital life." However, in a limited study made on this subject in a group of 12 young men and eight young women, the nonexistence of a different urinary excretion of 11 oxyketosteroids in the two sexes [12] was observed.

Our data with regard to the age at which rheumatic fever first attacks do not differ very much from those reported by other authors. In Mexico, this disease attacks principally children or young people, the average being 14.75 years of age and the peak being between 10 and 15 years (46.49% of the cases). In 69.35% of the cases, the onset was before 21 years. Schwentker [13] finds the peak at five to 10 years, but Lichwitz [14] reports that in 43.58% of the cases the onset occurred between 10 and 20 years, thus approaching our own figures. The former found that in 75% of the cases rheumatism was present under the age of 30 years, whereas we found that in 91.93% of our rheumatics the onset was before 21 years of age (figure 3).

Another point to be considered is that the genetic statistics of rheumatism which we made with Castillo should be corrected. In considering siblings up to the age of puberty, we certainly must have omitted the first attack occurring during the postpuberal age; that, if included, would have increased our figures at least 30% more, thereby increasing the proposed number to 100%.

In discussing the geographic distribution of rheumatism we find important data. The inaccuracy of a climatic definition based on a political division of the country into states and territories must be emphasized, but its approximate validity can be fairly stated. Thus we conclude that in all the sub divisions classified as having a temperate-rainy climate (the State of Mexico, the Federal District, Puebla, Tlaxcala, Guanajuato and Hidalgo), the rheumatic index is high (over 0.55).

The states with predominantly tropical-temperate-rainy climate (Michoacan, Jalisco, Guerrero, Morelos) occupy an intermediate position. The situation is similar for states with a dry climate (Nuevo Leon, Zacatecas, Chihuahua, Aguascalientes, San Luis Potosi, et cetera). It is interesting to note that the rheumatic index is always lower than 0.25 where a tropical-rainy climate predominates (Veracruz, Colima, Tamaulipas, Nayarit). Minimal values are shown for three states with absolute tropical climate (Tabasco, Chiapas, Nayarit), and for one which is characteristically dry (Sonora).

Our findings agree with the statement made by Coburn regarding the spontaneous improvement of rheumatism (rheumatic activity) in the tropics and its recurrence in temperate climates. In 1886 Hirsch [15] had already mentioned that rheumatic fever hardly existed in tropical countries (except those with plateaux).

Considering the above, we could set aside the important interference of extraclimatic, racial or economic-social factors. Tlaxcala and Chiapas, inhabited by similar proportions of pure-blooded and mixed Indians, show extremes in their values: 0.60 and 0.08, respectively. The Federal District, where the standard of living is probably the highest in the entire Republic, has the same climate as Tlaxcala, where the standard of living is much lower, but shows, nevertheless, similar r/t indices.

In our opinion, to find the cause of the phenomenon in which we are

interested it would be necessary to carry out investigations and studies along the following lines: (a) climate and streptococcal epidemiology (the investigation of carriers and behavior of antibodies in different climates), and (b) hypophysiocortical functioning and climatic adaption.

We have already discussed the seasonal nature of rheumatic activity in Mexico,[16] but as we lack sufficient data we cannot make absolute statements. What is epidemiologically confirmed in other countries which have temperate climate can also be applied to Mexico, that is, that a higher incidence of rheumatic attacks occurs during spring and at the end of summer, at which time the hemolytic streptococcus carriers and streptococcal infections reach their peak. In figure 4, different behavior in relation

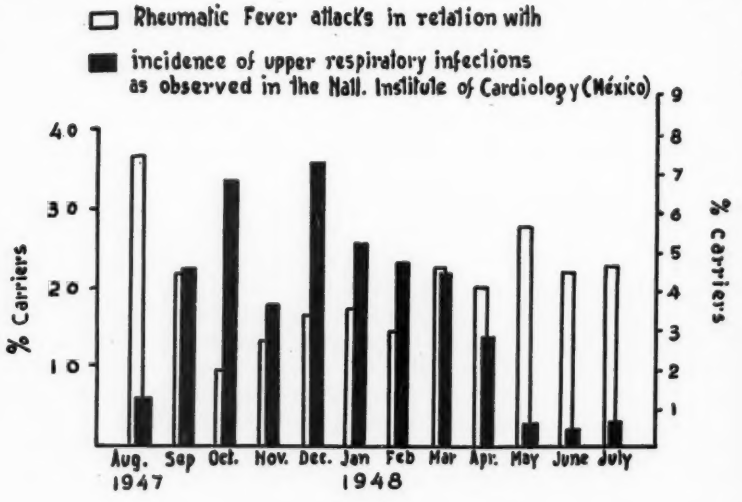

FIG. 4.

to the development of the upper respiratory infections, such as "grippe," is demonstrated. Once more, epidemiology of rheumatic fever tends to follow that of streptococcal infections and shows no relationship with "nonspecific" upper respiratory infections.

The data of the economic-social classification and the rheumatic frequency undoubtedly show the heretofore known fact that rheumatism preëminently attacks the socially needy classes. Professor Chavez pointed out that in the General Hospital 60% of the cardiacs were rheumatics. We now show a decrease in the rheumatic frequency from the index 0.41 in the poorest class (A) to those in better economic conditions (0.31). The difference between the two is statistically significant (X^2 of 6.70 for 1 D.F.) It is necessary to consider the adverse role of over crowding as a spreading

agent of the rheumatic virus (whatever it may be) when organizing and planning rheumatic prophylaxis.

From another viewpoint, the rheumatic ailments in our economic-social group rich in indigenous component become quite apparent. Since our investigations with Rugiero [17] we have noted that, as the economic-social status falls, the indigenous blood traits increase. The greater rheumatic incidence in the indigenous group should not be considered to be due to a greater genetic (racial) predisposition to rheumatism (which would not concur with its equivalent in other groups of white European-type populations); but rather shows that, in Mexico, judging from our own studies, the white or mixed-white population enjoys a better economic situation in comparison with that of the mixed or pure Indians. There might well be a possibility of presenting more substantial proofs along these lines, such as income *per capita*, housing conditions, nourishment, average life span, et cetera, and the rheumatic morbidity in the different racial groups. We submit our information as it represents some of the biological evidence obtained, and we believe it has an important objective value.

A decrease of rheumatism has been observed in the whole world. For instance, in Denmark,[18] where the disease is officially reported, the value was $30 \times 10{,}000$ in 1900 and in 1948 had diminished to $4.8 \times 10{,}000$. Comparative studies were made by Atwater in 1927, by Glover in 1930 and 1946 and, even more recently, by Quinn and Quinn.[19] It is interesting that the authors note less mortality in the younger group, where rheumatic activity is higher.

In analyzing our material it would seem that in Mexico there has been a noticeable decrease in the rheumatic index (figure 2), stressing that it is a real reduction in morbidity and not a contrivance to increase the total number of nonrheumatic cardiac consultations; as the denominator of our coefficient is higher, its increase does not correspond to that of the numerator, which since 1947 remains the same or has decreased (1950).

In the following table the first coefficient, 0.3974, found in 1944, is used as a reference point, but to simplify calculations an equivalent of 40% is given.

TABLE 4

Rheumatic Frequency in Mexico from 1944 to 1950, Inclusive
Number of Rheumatics

Year	r/t	Found	Expected	Difference
1944	0.3974	376	376	—
1946	0.2899	689	950	+261
1947	0.3742	929	992	− 63
1948	0.3501	918	1,048	−130
1949	0.3264	979	1,199	−220
1950	0.2201	781	1,357	−576

The apparent reason or reasons for a reduction of pharyngeal infections do not exist in Denmark, since in the past years these have increased there. Changes may possibly exist in the rheumatic virulence of the streptococcus strains which affect people nowadays. It is hard to prove this hypothesis, considering the difficulty in experimentally reproducing the rheumatic equivalent with streptococcus (although Swift [20, 21] and others have succeeded in doing so in animals). To establish an analogy, we can mention the case of tuberculosis: tuberculous morbidity has diminished considerably, notwithstanding the fact that the virulence of strains from clinical cases of over 50 years ago is comparable to that of strains obtained from recent cases. From this point of view it would be necessary to explain the phenomenon by changes or alterations in the host and not in the causative agent, which, of course, would not be due to genetic reasons. Another possibility could be the improvement of housing conditions and nourishment. Those interested in this problem will notice that, regarding Denmark, the figure of the Clemmensen paper shows an increase of rheumatism during war periods (World Wars I and II). It is also noteworthy that Quinn, in the United States of America, mentions a rheumatic mortality decrease in the North American white population. The decrease is less, however, in the Negroes, whose economic-social situation and standard of living contrast noticeably with those of the rest of the population.

The possible factor represented by chemotherapy and antibiotics, which have proved their prophylactic value [22, 23, 24, 25, 26] in rheumatic fever, is worth considering, but could not affect the record of the first 40 years of this century. Rheumatic morbidity has diminished in Denmark since 1900, long before the discovery of sulfa drugs and penicillin. At any rate, in our case the decrease occurred gradually during the first years and then became abrupt in 1950. This is likely to have been brought about through the intervention of a variable quite independent of the one represented by the improvement of the economic-social condition of the population studied. This calls to mind that subacute and chronic septicemias caused by streptococcus have almost vanished from our midst during the past two years—to be more exact, since the advent and more extensive use of penicillin; thus we can assume that the new antimicrobic drugs have exerted their influence in Mexico. In this respect, it would be interesting to compare our annual curves of incidence with those of investigators from other countries.

V. Summary and Conclusions

The following conclusions have been reached as the result of a thorough review of the records of the National Cardiological Institute since 1944:

A. Rheumatic heart disease is widespread in the Mexican Republic. Considering the rheumatic index, its prevalence is comparable to that found in temperate climates in such countries as England and the United States.

B. The presence of a large Indian component in the Mexican population is not considered significant in relation to rheumatic predisposition. If there are more rheumatics among the economically needy classes (having a greater indigenous component), the phenomenon should be attributed to the economic-social factor and not to the racial (genetic) traits.

C. It has been substantially proved that the female sex is more susceptible to rheumatism. This is noted during the prepuberal age as well as during the second and third decades of the feminine life, hence suggesting a greater hypophysiocortical instability in women, especially during their more active genital period.

D. Climate has a decisive influence on the development of rheumatism. When the variables constituted by the different genetic or economic factors are discarded, the very low rheumatic morbidity in tropical-rainy climate is noted, whereas it is very high in temperate-rainy zones, with a medium position in dry climate.

E. Rheumatism has decreased since 1947. The cause of this phenomenon can be attributed to improved living conditions in the Mexican Republic.

F. In Mexico, rheumatic heart disease produces about one third of the cases of cardiopathy. Therefore, a special campaign should be organized to prevent rheumatism and, in particular, the heart complications of this disease.

BIBLIOGRAPHY

1. Chavez, I.: Incidencia de las cardiopatías en México, Arch. latino am. de cardiol. y hemat. **12**: 87, 1942.
2. de Celis, E. R.: Datos sobre la incidencia de enfermedades cardiovasculares in Lima, Rev. Peruana de Cardiol. **1**: 277, 1952.
3. Cossio, cited by Chavez.[1]
4. de Morais, F. R., and de Amorim, I.: Incidencia etiológica de cardiopatías na Cidade de Recife, Arq. Brasil. Cardiol. **5**: 316, 1952.
5. Osorio, J. A., and Utinguassu, O.: Estudio etiológico das cardiopatías no Rio Grande do Sul, Arq. Brasil. de Cardiol. **5**: 307, 1952.
6. Suárez, cited by de Celis.[2]
7. Tranchesi, B., Nussenzveig, I., Tranchesi, J., Cavalheiro Dias, J., Tisi, O. G., and Fabio Lion, M.: A etiologia das cardiopatias em Sao Paulo, Brazil, Arq. Brasil. Card. **4**: 31, 1951.
8. Wilson, M. G.: Rheumatic fever, 1940, The Commonwealth Fund, New York.
9. Salazar-Mallén, M., and Castillo, F.: Genética del reuma cardioarticular, Arch. Inst. cardiol. México **23**: 3, 1952.
10. Vivó, J. A.: Geografía de México, 1949, Fondo de Cultura Económica, México.
11. Gold, S. C.: An hypothesis concerning the pathogenesis of systemic lupus erythematosus, Brit. J. Dermat. **65**: 43, 1953.
12. Talbot, N. D., Albright, F., Saltzman, A. H., Zygmuntowicz, A., and Wixom, R.: The excretion of 11-oxycorticosteroid-like substances by normal and abnormal subjects, J. Clin. Endocrinol. **7**: 33, 1947.
13. Schwentker, F. F.: Epidemiology of rheumatic fever, *in* Rheumatic fever, Minnesota Heart Association, 1952, University of Minnesota Press, Minneapolis.

14. Lichwitz, L.: Rheumatic fever, 1944, Grune & Stratton, New York.
15. Hirsch, mentioned by Nichol, S. *in* Rheumatic heart disease in Southern Florida, Am. Heart J. **9**: 63, 1933.
16. Salazar-Mallén, M., and Gurria Davo, J.: Estreptococo en la flora faríngea, Arch. Inst. cardiol. México **19**: 298, 1949.
17. Rugiero, C.: Tésis recepcional, 1953, Escuela N. de Ciencias Biológicas, México.
18. Clemmensen, S.: Rheumatic fever statistics in Denmark from 1878 to 1946, and their significance in prophylaxis, Acta med. Scandinav. suppl. **234**: 109, 1949.
19. Quinn, R., and Quinn, J.: Decline in mortality in acute rheumatic fever in New Haven, Connecticut, 1920–1938, New England J. Med. **245**: 211, 1951.
20. Murphy, G., and Swift, H.: Induction of heart lesions closely resembling those of rheumatic fever in rabbits, following repeated skin infection with group A streptococci, J. Exper. Med. **85**: 687, 1947.
21. Murphy, G., and Swift, H.: The induction of rheumatic-like cardiac lesions in rabbits by repeated focal infections with group A streptococci. Comparison with the cardiac lesions of serum disease, J. Exper. Med. **91**: 485, 1950.
22. Houser, H. B., Wannamaker, L. W., Rammelkamp, C. H., Denny, F. W., Brink, W. R., Hahn, E. O., and Dingle, J. H.: Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of penicillin, J. Lab. and Clin. Med. **36**: 839, 1950.
23. Wannamaker, L. W., Rammelkamp, C. H., Jr., Denny, F. W., Brink, W. R., Houser, H. B., Hahn, E. O., and Dingle, J. H.: Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin, Am J. Med. **10**: 673, 1951.
24. Bundy, W. E., McCue, C. M., and Porter, R. R.: The control of rheumatic fever recurrences with sulfadiazine and Gantrisin, J. Pediat. **41**: 320, 1952.
25. Kohn, K. H., and Milzer, A.: Prophylaxis of recurrence of rheumatic fever with penicillin, J. A. M. A. **151**: 347, 1953.
26. Roberts, E.: Use of sulfonamides and penicillin to prevent recurrence of rheumatic fever, Am. J. Dis. Child. **85**: 643, 1953.

PULMONARY LESIONS IN DISSEMINATED LUPUS ERYTHEMATOSUS *†

By Don C. Purnell, M.D., Archie H. Baggenstoss, M.D., and Arthur M. Olsen, M.D., F.A.C.P., *Rochester, Minnesota*

Pathologists and clinicians have been aware for many years that pulmonary and renal complications are often terminal events in the life history of the patient suffering from disseminated lupus erythematosus. A considerable body of knowledge has accumulated concerning the essential features of the renal lesions in this variegated syndrome. Likewise, it has been a well-known fact that pyogenic bronchopneumonia is a lesion frequently found at necropsy in these patients.

The presence of pulmonary disease of other types manifested at various times throughout the course of this condition has, however, been emphasized only in the relatively recent past. In 1904 Osler [1] described a patient with lupus erythematosus in whom lobar pneumonia developed. Despite a protracted course he recovered completely, only to die a few months later in uremia. Clinical data collected over the course of half a century since then have repeatedly demonstrated the presence of varied pulmonary findings during the active course of this disease. That these data may be difficult to substantiate objectively is suggested by the report of Sante and Wyatt,[2] who stated that patients with disseminated lupus erythematosus, scleroderma and dermatomyositis are without pulmonary involvement, radiographically, until the terminal stages of the disease. The difficulty of determining the nature of many of these pulmonary changes during the life of the patient has been stressed by Klemperer and co-workers,[3] who have stated: "The post-mortem observations do not properly reflect the remarkable clinical manifestations of pulmonary involvement in this disease—the bouts of waxing and waning, migrating bronchopneumonia."

Much of our information, however, must still be obtained from carefully documented necropsy material. In time, advances in radiologic technic or more widespread investigative use of such procedures as biopsy of the lung may provide more precise information regarding the changing pattern of pulmonary involvement.

This study was inaugurated in an effort to determine the frequency of the various types of gross and histologic lesions which may be present in the lungs of a series of patients dying of disseminated lupus erythematosus.

* Received for publication July 6, 1954.

† Abridgment of thesis submitted by Dr. Purnell to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

From the Mayo Foundation and the Sections of Pathologic Anatomy and Medicine of the Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

It was also hoped that additional data could be obtained in regard to the peculiar interstitial mucinous edema described by Baggenstoss [4] as occurring in the lungs of a patient with this syndrome.

Historical Review

Klemperer and co-workers credited the original description of the syndrome of disseminated lupus erythematosus to Hebra in 1845. According to Gahan,[5] Cazenave in 1851 named the condition "lupus erythematosus." He believed it to be a variant of lupus vulgaris, and ascribed no effect on the general condition of the patient to this syndrome. Also according to Gahan,[5] Kaposi first reported in 1872 that the lesions could assume a generalized form with a fatal outcome. He related necropsy findings, attributing death to intercurrent pneumonia in certain patients and tuberculosis in others. Libman and Sacks [6] described the morbid anatomy in considerable detail in 1924, and reported on a verrucous nonbacterial mural and valvular endocarditis.

Baehr and co-workers [7] in 1935 said that the protean nature of this syndrome and the involvement of multiple systems could best be explained on the basis of diffuse endothelial inflammation of the capillaries, arterioles and venules of the various tissues. These changes were noted in conjunction with verrucous endocarditis in several instances. Jarcho [8] in 1936 demonstrated the "onion-skin" periarteriolar fibrosis in the spleens of patients diagnosed as having acute disseminated lupus erythematosus. It has been subsequently demonstrated that this change is not a specific pathognomonic lesion in disseminated lupus erythematosus.

Klemperer and co-workers [3] in 1941 advanced the concept that the essential pathologic alteration in disseminated lupus erythematosus is a physicochemical alteration of the interfibrillary ground substance of collagenous connective tissue. This change, known as "fibrinoid degeneration," had been described originally in 1880 by Neumann. The essential features of this change were given as homogenization and an eosinophilic tinctorial reaction of the ground substance, plus straightening and thickening of the connective-tissue fibers. The presence of this change in the basement membrane of the glomerular tufts gave rise to the designation of the "wire-loop" renal lesion.

Rakov and Taylor [9] and Foldes [10] described interstitial inflammatory lesions of the lung with atelectasis attributed to these lesions. Teilum [11] discussed "focal allergic pneumonia" in this syndrome, and described fibrinoid necrosis in the connective tissue and in the capillary walls of the interalveolar septa.

Baggenstoss [4] observed a peculiar basophilic interstitial mucinous edema in association with interstitial pneumonitis and alveolar hemorrhage in a case of disseminated lupus erythematosus, and presented the hypothesis that

this mucinous change might be related to the interstitial pneumonia with atelectasis described by Rakov and Taylor, perhaps in the role of a precursor.

Material and Methods

Necropsy data were available on 54 patients with a pathologic diagnosis of disseminated lupus erythematosus. For this study the following criteria were utilized in establishing the diagnosis: (1) compatible clinical history, (2) presence of microscopic visceral lesions in the kidneys, spleens and skin, and (3) presence of the L. E. phenomenon in the peripheral blood or bone marrow of those patients studied since 1948. The presence of the first two criteria was considered essential for inclusion in this series.

Table 1

Incidence of Pulmonary Lesions in 54 Cases of Disseminated Lupus Erythematosus

Lesion	Cases		Per Cent	
Bronchopneumonia	41		75.9	
Hemorrhage	36		66.6	
Pleural effusion	36		66.6	
Unilateral		10		18.5
Bilateral		26		48.1
Pulmonary edema	30		55.5	
Interstitial pneumonia	29		53.6	
Diffuse		24		44.3
Focal		5		9.2
Congestion	28		51.8	
Atelectasis	24		44.3	
Diffuse		15		27.7
Focal		9		16.6
Acute pleuritis	23		42.6	
Pleural fibrosis	19		35.2	
Acute bronchitis	15		27.7	
Organizing pneumonia	10		18.5	
Mucinous edema	9		16.6	
Abscess	9		16.6	
Tuberculosis	9		16.6	
Active		3		5.5
Healed		6		11.1
Pulmonary infarction	3		5.5	
Empyema	2		3.7	
Bronchiectasis	2		3.7	
Emphysema	1		1.8	
Lobar pneumonia	1		1.8	
Bronchial adenoma	1		1.8	
Calcified cyst	1		1.8	

Protocols of examinations, gross specimens and histopathologic material were available for study. Where additional data were required, new slides were prepared and supplemental staining technics were utilized. Special stains for mucin, the periodic acid-Schiff stain, and the elastic-van Gieson stain were used to demonstrate the nature of certain lesions.

There were 47 females, whose ages ranged from nine to 66 years, and seven males, whose ages ranged from 19 to 54. The series represented patients coming to necropsy at the Mayo Clinic for the period 1925 through 1952.

Pathology of Pulmonary Lesions

The various pulmonary lesions noted in this study are presented in the table according to type and incidence. As previous authors have noted, terminal bronchopneumonia was the most common finding, being present in one or more lobes in 41 cases (75.9%). There were no distinct or unusual histopathologic features that could be used to differentiate this from other forms of bronchopneumonia. Antemortem hemograms revealed in most instances adequate leukocytic response to the infection, usually in excess of 10,000 leukocytes per cubic millimeter of blood.

Hemorrhage, observed in 36 cases (66.6%), was variable as to its extent and location. The lesions varied from a few focal, subpleural petechial hemorrhages to massive hemorrhage involving an entire lung. Although occasionally these changes were observed in conjunction with purpuric areas on the skin and objective changes in the bleeding and clotting mechanisms, they were usually present with no readily demonstrable etiologic predecessor and were assumed to be the result of damage to capillary walls. A hemorrhagic component to the exudate in many of the cases of bronchopneumonia was quite common.

Pleural effusion was noted bilaterally in 26 cases (48.1%) and unilaterally in 10 cases (18.5%). Quantities of fluid in excess of 100 c.c. were considered evidence of pleural effusion. Amounts of a liter or more were the usual findings, and more massive effusions were not uncommon. The fluid was clear and yellow in most instances, only rarely being designated as "turbid" or "fibrinous" in type.

Pulmonary edema, which occurred in 30 cases (55.5%), was associated with a clinical diagnosis of congestive heart failure in five cases and with vasomotor collapse in three cases. As was true in the hemorrhagic lesions, no specific inciting factor could be determined for the majority of cases. While the histopathologic features of the capillaries in the lungs were not remarkable in these instances, the factor of increased capillary permeability was similarly postulated.

Inflammatory exudates within the substance of the alveolar walls and interstitial connective-tissue septa were noted in a diffuse distribution in 24 cases (44.3%), and in isolated focal areas in five cases (9.2%). These changes were usually inconspicuous at necropsy, being diagnosed grossly in only two instances. In 17 cases in which inflammation of the alveolar walls was demonstrated, fibrinous exudates and inflammatory cells within the alveolar spaces were also present. In many instances this undoubtedly represented spread along the alveolar walls and the septa of an inflammatory process which began within the alveolar spaces. Atelectasis of variable degree and extent occurred in 15 cases showing such interstitial inflammatory exudates, but the presence of hydrothorax or tracheobronchial mucous plugs, or both, in 13 of these cases made difficult an assessment of the role of the interstitial pneumonia with atelectasis described by Rakov and

Taylor [9] and Foldes.[10] There can be little doubt that thickening of alveolar walls with an inflammatory exudate can predispose to distortion of the alveolar architecture.

The inflammatory reaction within the alveolar walls consisted of the exudation of fibrin and infiltration with polymorphonuclear leukocytes, large mononuclear phagocytes and occasional lymphocytes and plasma cells.

It is sometimes difficult to determine whether the pulmonary congestion observed at necropsy was an essential part of the patient's illness or merely an agonal development. Its significance when present is therefore singularly difficult to evaluate. The role of a recumbent position maintained for a long time, the occurrence of left ventricular failure, and the known widespread vascular damage in disseminated lupus erythematosus make an assessment of this finding difficult. The presence of dilated capillaries and veins was apparent in 28 cases (51.8%). Such changes were routinely manifested in cases in which there was pulmonary edema.

Diffuse atelectasis of one or more lobes in one or both lungs occurred in 15 cases (27.7%), and focal areas of collapse were seen in nine cases (16.6%). Additional focal areas of collapse were seen in each of the cases demonstrating diffuse atelectasis. The association of pleural effusion and mucous plugs with atelectasis has been mentioned previously.

Acute fibrinous pleuritis appeared in 23 cases (42.6%). A purulent component of the inflammation was noted in one case, and focal areas of necrosis within the fibrinous exudate occurred in another case. Early attempts at organization of the exudate were common. The association of acute fibrinous pleuritis with bronchopneumonia was, as one might anticipate, very frequent. Evidence of previous pleural inflammation in the form of pleural fibrosis and thickening was seen in 19 cases (35.2%). Not infrequently, acute inflammation and pleural fibrosis occurred concomitantly in the same case, testifying to multiple episodes of involvement.

Inflammation in the respiratory tract, manifested as acute purulent bronchitis, formed a part of the pathologic picture in 15 cases (27.7%). A mucopurulent exudate containing polymorphonuclear leukocytes within the lumen and infiltration of the bronchial mucosa and submucosa with similar cells formed the essential features of this lesion.

Regions of bronchopneumonia undergoing organization of the alveolar exudate were observed in 10 cases (18.5%). A terminal respiratory infection was noted clinically in these cases. No instance of marked organization with carnification was seen in this series.

The most interesting and unusual lesion noted in these cases was a mucinous edema appearing in the connective tissue of the alveolar walls and in perivascular and peribronchiolar tissues. This finding was noted in nine cases (16.6%) and usually in conjunction with interstitial pneumonitis and alveolar hemorrhage (figure 1). With the hematoxylin-eosin tissue stain a basophilic appearance is given to the connective tissue around capillaries, small arterioles and bronchioles. The tissue thus affected appears irregu-

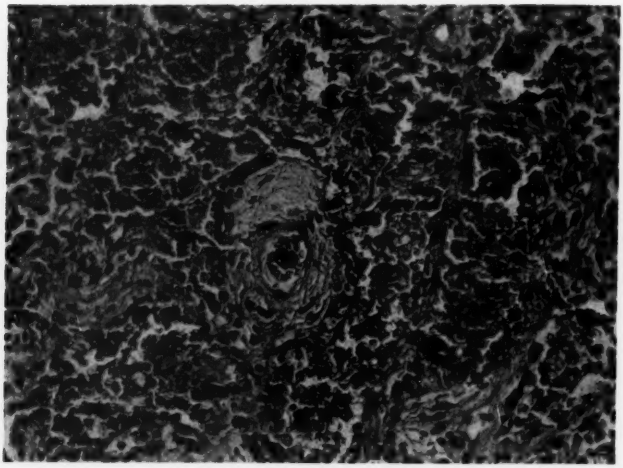

FIG. 1. Perivascular mucinous edema with alveolar hemorrhage (mucicarmine stain; × 200).

lar, vacuolated and often finely granular. From these areas extension along the alveolar walls occurs, giving a lattice-like network (figures 2 and 3). Stains for mucin give a positive reaction in these lesions. Numerous mucin stains as controls were performed on pulmonary tissues from patients with disseminated lupus erythematosus that did not reveal the basophilic lesion

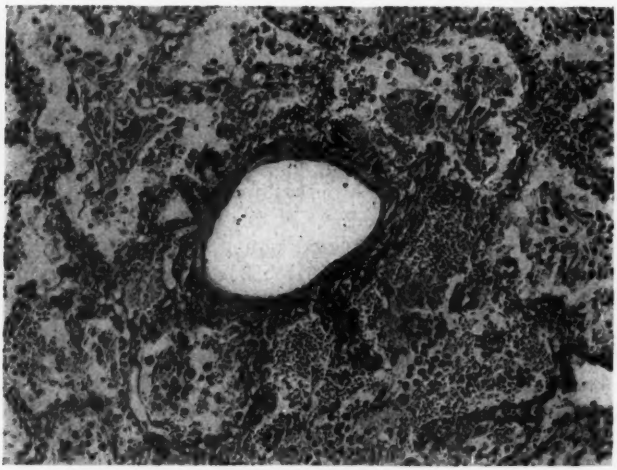

FIG. 2. Perivascular mucinous edema with vacuolation and irregularity of connective tissue (mucicarmine stain; × 150).

described above, and from patients coming to necropsy because of other fatal conditions. No mucinous edema was noted in any of the controls.

Baggenstoss has hypothesized that this lesion may represent a precursor of interstitial pneumonitis. One patient showing interstitial mucinous edema of the pulmonary tissue also was demonstrated to have a similar basophilic lesion of the connective tissue in the mitral valve, in the pericardium and in the periarticular connective tissue about the shoulder joint. It is of interest that no evidence of fibrinoid degeneration or necrosis was noted in the pulmonary tissues of the cases in this series, but the mucinous edema occurred only in the connective tissue. We have also observed this

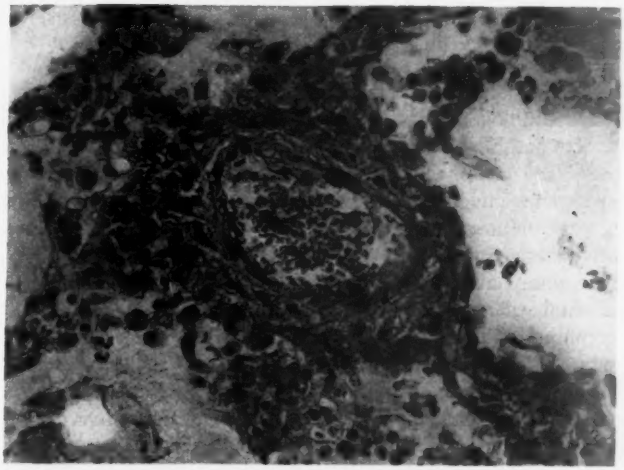

FIG. 3. Perivascular mucinous edema with extension along alveolar walls (mucicarmine stain; × 250).

interstitial mucinous edema in the same distribution in the lung of a patient with periarteritis nodosa.

Pulmonary abscess formation occurred in conjunction with bronchopneumonia in nine cases (16.6%). Usually this was manifested in the form of several small abscesses within an area of pneumonic consolidation. The liquefaction necrosis differed in no way from abscess formation occurring in patients with other diseases.

Calcified hilar nodes and primary Ghon complexes were noted in six cases (11.1%). Acute miliary tuberculosis was found in two cases, in one of which the onset occurred during therapy with cortisone. One patient with active caseous pulmonary tuberculosis was examined.

Pulmonary infarction appeared in three cases (5.5%). In two of these cases the infarction occurred at sites affected secondarily by bronchopneumonia, and abscess formation then took place at the site of the original

infarction. Evidence of pulmonary arterial embolization was found in one case, but a source for the emboli in the peripheral veins could not be determined in any of the cases. Pulmonary congestion was a prominent finding in each of the three cases.

Empyema occurred in only two cases (3.7%). This seemed rather unusual in the face of the frequent occurrence of pyogenic bronchopneumonia and the not infrequent occurrence of pulmonary abscesses.

Bronchiectasis complicated other pulmonary lesions, especially bronchopneumonia, in two cases (3.7%). No unusual or distinctive features were observed in any of the single cases of emphysema, lobar pneumonia, bronchial adenoma and calcified pulmonary cyst.

Comment

The protean manifestations of disseminated lupus erythematosus, both clinical and pathologic, have been amply documented in the literature. Similarly, the pathologic lesions in the pulmonary tissues have been described for many years, with principal interest having centered about the terminal pyogenic infections. Less attention seems to have been directed toward a total picture of the varying lesions found in these patients and their relative frequencies.

In more than half the cases studied, bronchopneumonia, hemorrhage, pleural effusion, edema, interstitial pneumonia or congestion, frequently in various combinations, was demonstrated, and these must be viewed as the most common lesions in a series of necropsy cases. These results are quite similar to those of other authors. The evidence of atelectasis in various degrees (44.3%) is primarily related to pleural effusion in a large number of cases, though bronchial obstruction by mucus was not uncommon.

Of considerable interest is the fact that no changes resembling fibrinoid necrosis were seen in the ground substance or connective-tissue fibers within the pulmonary tissues. The alterations of these collagenous elements in other organs of patients with disseminated lupus erythematosus have been considered the basic pathologic denominator. The finding of a basophilic mucinous edema affecting connective tissue around blood vessels and bronchioles and present in interstitial connective tissue arouses some speculation with regard to a possible relationship between mucinous edema and deposition of fibrinoid material.

Altshuler and Angevine [12] noted that in mucinous edema there was an increase in acid mucopolysaccharides, and that the common feature of fibrinoid formation was precipitation of acid mucopolysaccharide of the ground substance of connective tissue. These authors described an early stage of mucinous edema in the development of fibrinoid degeneration in the Aschoff nodule of rheumatic fever. Later stages were characterized by the presence of a fine fibrillar precipitate and a fusion into homogeneous bands, then breakdown into granular masses. Experimentally, Selye [13] produced mu-

cinous edema in the skin of a hairless mouse by repeated local application of estradiol. Whether the mucinous edema in the lungs, pericardium, mitral valve and periarticular connective tissue described in our study bears a relationship to fibrinoid necrosis remains an interesting problem for further histochemical study.

Summary and Conclusions

A pathologic study of the gross and microscopic pulmonary lesions in 54 cases of disseminated lupus erythematosus was made and the results were tabulated in an effort to demonstrate the wide range of abnormalities that can occur. Special attention was directed toward the basophilic mucinous edema occurring in the perivascular and peribronchiolar connective tissues and the alveolar wall. The relative frequency of this change (16.6%) in the group studied and the absence of fibrinoid degeneration are of some interest. A possible histochemical relationship between mucinous edema and fibrinoid formation, based upon precipitation of acid mucopolysaccharides in the connective-tissue ground substance, has been suggested.

On the basis of the data presented, the following conclusions seem warranted:

1. Pulmonary lesions occur commonly in patients with disseminated lupus erythematosus.

2. Secondary infection and vascular damage account for the changes most frequently noted.

3. There is no pathognomonic pulmonary lesion in this syndrome.

4. Basophilic mucinous edema affects peribronchiolar, perivascular and interstitial connective tissues of the lung, but also has been described in connective tissues of other organs in this syndrome.

BIBLIOGRAPHY

1. Osler, W.: On the visceral manifestations of the erythema group of skin diseases [Third Paper], Am. J. M. Sc. **127**: 1, 1904.
2. Sante, L. R., and Wyatt, J. P.: Roentgenological and pathological observations in antigenic pneumonitis: its relationship to the collagen diseases, Am. J. Roentgenol. **66**: 527, 1951.
3. Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosus, Arch. Path. **32**: 569, 1941.
4. Baggenstoss, A. H.: Visceral lesions in disseminated lupus erythematosus, Proc. Staff Meet., Mayo Clin. **27**: 412, 1952.
5. Gahan, E.: Original description of lupus erythematosus, Arch. Dermat. and Syph. **66**: 458, 1952.
6. Libman, E., and Sacks, B.: A hitherto undescribed form of valvular and mural endocarditis, Arch. Int. Med. **33**: 701, 1924.
7. Baehr, G., Klemperer, P., and Schifrin, A.: A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis), Tr. A. Am. Physicians **50**: 139, 1935.
8. Jarcho, quoted by Dubois, E. L.: Systemic lupus erythematosus, M. Clin. North America **36**: 1111, 1952.

9. Rakov, H. L., and Taylor, J. S.: Acute disseminated lupus erythematosus: without cutaneous manifestations and with heretofore undescribed pulmonary lesions, Arch. Int. Med. **70**: 88, 1942.
10. Foldes, J.: Acute systemic lupus erythematosus, Am. J. Clin. Path. **16**: 160, 1946.
11. Teilum, G.: Pathogenetic studies on lupus erythematosus disseminatus and related diseases, Acta med. Scandinav. **123**: 126, 1946.
12. Altshuler, C. H., and Angevine, D. M.: Histochemical studies on the pathogenesis of fibrinoid, Am. J. Path. **25**: 1061, 1949.
13. Selye, H.: Effect of folliculoid hormones on abnormal skin: further observations of the effect of estradiol on the skin of mice of the rhino, hairless and naked strains, Arch. Dermat. and Syph. **50**: 261, 1944.

THE EFFECTS OF BREATHING 99.6% OXYGEN ON PULMONARY VASCULAR RESISTANCE AND CARDIAC OUTPUT IN PATIENTS WITH PULMONARY EMPHYSEMA AND CHRONIC HYPOXIA *

By Russell H. Wilson, M.D., Ph.D., *Dallas, Texas,* Wayne Hoseth, M.D.,† and Mary E. Dempsey, M.S.†
Minneapolis, Minnesota

It is well established, experimentally, that acute hypoxia causes a significant elevation of the pulmonary arterial blood pressure. The magnitude of the rôle of chronic hypoxia in increasing the pulmonary vascular resistance leading to increased pressure in the lesser circulation has not been clearly defined. Efforts have been made to separate the effects of changes in the magnitude of cardiac output and pulmonary vascular resistance on the pulmonary arterial pressure, but the relationship of each phenomenon to acute and chronic pulmonary hypertension has not been clearly established.

Von Euler and Liljestrand [1] found that in cats the pulmonary arterial pressure increased while the cats were breathing 10% oxygen. The cardiac output was not measured during the period the pressures were recorded; therefore, it was not possible to separate the effect of increased flow from change in pulmonary vascular resistance.

Motley and his associates [2] studied the results of hypoxia on the pulmonary arterial pressure in five normal males. They demonstrated an increase in the pressure with a simultaneous decrease in the cardiac output during acute hypoxia. Westcott and his associates [3] studied the effect of hypoxia on the cardiac output and found no statistically significant change in the group of experimental subjects as a whole. They found a significant rise in pulmonary vascular resistance and pulmonary arterial pressure.

Liljestrand [4] showed that acute hypoxia increased the pulmonary arterial pressure. He presumed the increase in flow was of insufficient magnitude to affect the pulmonary arterial pressure. He did not estimate the cardiac output. He observed that acute hypoxia and increased P_aCO_2 had concordant effects on the pulmonary arterial pressure.

Harrison [5] states that low P_aO_2 increases the cardiac output, which is in contradistinction to the impression given by other data.[2] Wiggers and associates [6, 7] remark that hypoxia increases the cardiac output by redistri-

* Received for publication May 10, 1954.
From the Department of Medicine of the Southwestern Medical School of the University of Texas, Dallas, Texas, and the Veterans Administration Hospital, McKinney, Texas.
† From the Veterans Administration Hospital, Minneapolis, Minnesota.

bution of blood and by cardiac acceleration. They also call attention to the fact that during hypoxia the ventricle ejects the blood with a greater economy of effort.

In view of the differences of opinion regarding cardiac output and its effect on the pulmonary arterial pressure in the presence of acute hypoxia and the relative absence of studies during chronic hypoxia, the following study was done to collect data in patients with pulmonary emphysema with chronic hypoxia while breathing 99.6% oxygen.

TABLE 1

Criteria for Selection of the 21 Patients with Chronic Pulmonary Emphysema

	Mean Values
Age—years	56.3
Body surface—sq. m.	1.68
Vital capacity—c.c. (A)	1930
Residual volume—c.c.	3640
One-second expiratory volume—c.c. (B)	952
Ratio B/A	49.4
Pulmonary alveolar nitrogen retention—%	4.1

METHOD

Twenty-one patients with severe chronic diffuse pulmonary emphysema and chronic hypoxia (table 1) were selected for study of the effect of breathing 99.6% oxygen on the cardiac output, pulmonary arterial pressure and total pulmonary vascular resistance. The alveolar nitrogen retention was estimated by the open circuit method of Darling and associates.[8] After the patients had been thoroughly prepared psychically, the right hearts were catheterized by the method of Cournand.[9] Pressures were recorded with a Statham Pressure Transducer and Sanborn Poly-Viso Recorder. The wedge pressures were recorded with the precautions previously published.[10] Oxygen uptake was determined by the gas analysis method of Haldane.[11] The respiratory minute volume was measured with the Tissot spirometer. Peripheral and pulmonary arterial blood samples were collected for arteriovenous oxygen differences before the period of oxygen breathing.[12] The per cent saturation of the arterial blood was measured as outlined in a previous publication.[13] The pH was measured at 38° C. with the glass electrode.[14] P_aCO_2 was calculated from the nomogram of Singer and Hastings.[15] Following these procedures, the patient was allowed to reach a steady state (as steady a state as a patient with emphysema is able to obtain). The patients breathed 99.6% oxygen for 20 minutes. Oxygen uptake was measured during the final minutes of this period with a recording spirometer. Samples of blood were collected for pH, arteriovenous oxygen differences, P_aCO_2, and per cent arterial oxygen saturation as outlined prior to oxygen breathing. The pressures were again recorded in the pulmonary arterial wedge, the right ventricle and the pulmonary artery.

Total pulmonary vascular resistances were calculated before and during the latter part of the oxygen-breathing period by the formula [16]

$$TPR = \frac{PA}{CO} \times 1332$$

where TPR = total pulmonary resistance in dynes sec cm^{-5}
PA = pulmonary arterial mean pressure
CO = cardiac output in cubic centimeters per second
1332 = conversion factor from mm. Hg to dynes per cm^5.

The statistical formulae and probability tables used in this study were those of Fisher.[17] The t test used in this study was to test the significance of difference from zero of the mean difference between samples.[17]

Results

The mean values and standard deviations of the complete data collected during this study are included in tables 1 and 2.

Table 2

Mean Values and Standard Deviations in 21 Patients of the Cardiac Output, Pulmonary Arterial and Wedge Pressures, and Pulmonary Vascular Responses While Breathing Ambient Air and 99.6% Oxygen

	Breathing Ambient Air	Breathing Oxygen 99.6 Per Cent
Respiratory volume—liters/minute	9.0 ± 2.5	6.0 ± 1.2
Cardiac output—liters/minute	5.6 ± 1.81	4.8 ± 1.77
Pulmonary arterial pressure—mm. Hg	25.2 ± 11.9	19.9 ± 9.7
Pulmonary arterial wedge pressure—mm. Hg	5.2 ± 2.3	4.1 ± 2.1
Total pulmonary vascular resistance—dynes cm. $sec.^{-5}$	417.2 ± 281.5	366.4 ± 111.5
Oxygen saturation arterial hemoglobin—%	80.3 ± 0.760	99.2 ± 0.58
Carbon dioxide tension of arterial blood—mm. Hg	47.7 ± 8.2	60.5 ± 6.7
pH whole arterial blood	7.38 ± 0.01	7.29 ± 0.02

The average age of the 21 patients studied was 56.3 years. All had severe emphysema and chronic hypoxia. The average alveolar retention of nitrogen after breathing oxygen for seven minutes was 4.1%, and the average residual volume was 3640 c.c. The mean one-second expiratory volume was 49.4% of the total vital capacity for the group. Thus it is shown that all patients had severe pulmonary emphysema. The mean arterial oxygen unsaturation varied from 11.0% to 44.0%. The active hemoglobin was completely physiologically saturated after breathing 99.6% oxygen for 20 minutes. The values are corrected for dissolved oxygen.

The minute volume decreased from 9 liters while the patients were breathing ambient air to 6 liters per minute while they were breathing 99.6% oxygen; $t = 7.5$, $p < 0.01$. During the oxygen-breathing period the P_aCO_2 increased from 47.7 mm. Hg to 60.5 mm. Hg; $t = 9.9$, $p < 0.01$. The pH of the arterial blood decreased from 7.38 to a mean of 7.29; $t = 13.3$, $p < 0.01$.

The average cardiac output changed from 5.53 liters per minute to 4.84 liters; $t = 2.34$, $p < 0.05$ (figure 1). There was correlation between the

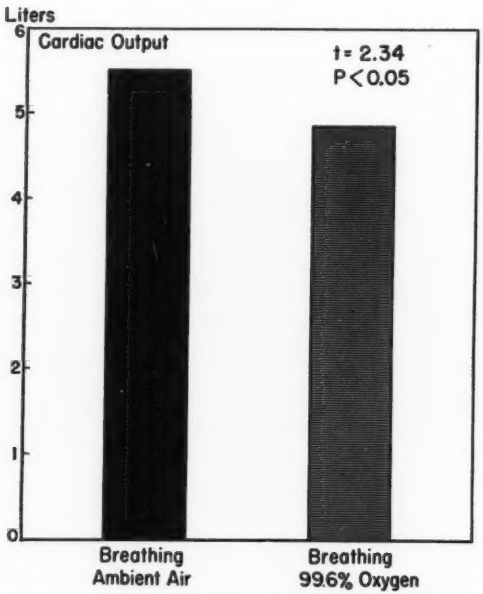

FIG. 1. The cardiac output in liters per minute breathing ambient air and 99.6% oxygen.

fall of the output of the heart and the change in percentage oxygen saturation of the blood in the 21 patients with pulmonary emphysema with varying degrees of hypoxia (table 3). Although the cardiac output fell slightly, there was no correlation between the decrements of blood flow and pulmonary vascular resistance; $r = 0.1511$, $p > 0.5$ (table 4). On the other hand, there was highly significant correlation between the mean total cardiac output and total mean pulmonary vascular resistance on ambient air and oxygen.

The mean total pulmonary vascular resistance decreased from 417.2 dynes cm sec^{-5} to 366.4 dynes cm sec^{-5} after the patients had been breathing oxygen for 20 minutes; $t = 14.9$, $p < 0.01$ (figure 2).

TABLE 3

Correlation Coefficients among the Change of Percentage Oxygen Saturation of the Arterial Blood, Cardiac Output and Decrement of the Mean Pulmonary Arterial Pressure

r_{12}*	0.1679	$p > 0.5$
r_{13}	0.7419	$p < 0.01$
r_{23}	0.5539	$p < 0.01$
$r_{12.3}$	0.7364	$p < 0.01$
$r_{13.2}$	0.7905	$p < 0.01$

* Number 1 refers to change in percentage oxygen saturation; 2, change in cardiac output; 3, change in mean pulmonary arterial pressure.

TABLE 4

Correlation Coefficients among the Percentage Oxygen Saturation of the Blood, Total Pulmonary Vascular Resistance and Cardiac Output Using the Partial Correlation Method of Analysis

r_{12}*	0.1679	$p > 0.5$
r_{13}	0.8868	$p < 0.01$
r_{23}	0.1511	$p > 0.5$
$r_{12.3}$	0.0800	$p > 0.5$
$r_{13.2}$	0.8880	$p < 0.01$

* Number 1 refers to change in percentage oxygen saturation; number 2, change in cardiac output; number 3, change in total vascular resistance while breathing 99.6% oxygen.

To determine correlation among the change in percentage oxygen saturation of the blood, change in total pulmonary vascular resistance and cardiac output, the partial correlation [17] method of analysis was used (table 4). There was significant correlation between the increment of oxygen saturation of the blood and the decrement of pulmonary vascular resistance.

To determine the correlation among the change in percentage oxygen saturation of the arterial blood, change in the mean pulmonary arterial pressure and change in cardiac output, the partial correlation method was again used, and the results are shown in table 3. There was significant correlation among the three variables when the effects of each on the other were demonstrated by the partial correlation formula.

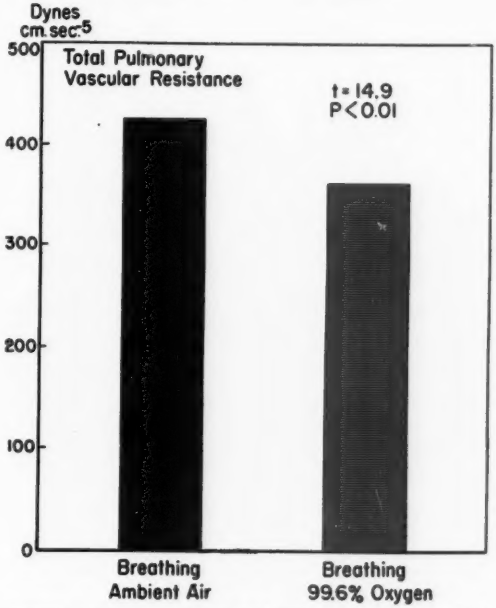

FIG. 2. The mean total pulmonary vascular resistance in dynes cm sec^{-5} breathing ambient air and 99.6% oxygen.

Concomitant with the small decrease in cardiac output, the mean pulmonary arterial pressure decreased from 25.2 mm. Hg to 19.9 mm. Hg; $t = 4.46$, $p < 0.01$ (figure 3). There was close correlation between the fall in pulmonary arterial pressure and rise in the percentage oxygen saturation of the arterial blood; $r = 0.7419$, $p < 0.01$. The mean pulmonary arterial wedge pressure decreased from 5.16 mm. Hg to 4.03 mm. Hg; $t = 9.17$, $p < 0.01$. There was no correlation between the increment of P_aCO_2 and the decrement of the pulmonary vascular resistance while the patients were breathing oxygen; $r = 0.04$, $p > 0.5$. There was a highly significant cor-

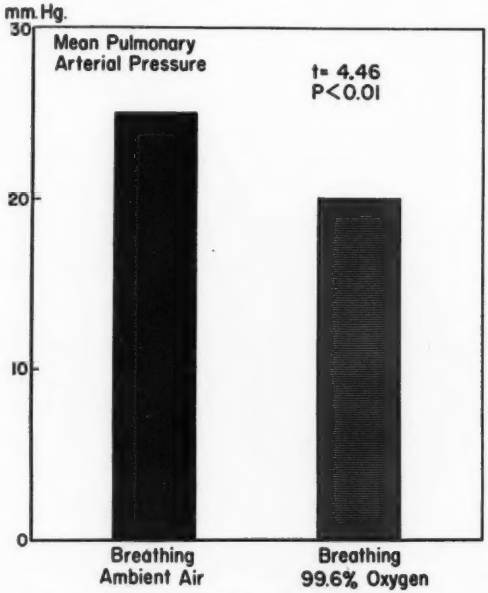

FIG. 3. The mean pulmonary arterial pressure breathing ambient air and 99.6% oxygen.

relation between the P_aCO_2 and pulmonary arterial pressure while they were breathing room air; $r = .5633$, $p < 0.01$. No demonstrable relationship was found between the fall of the pH of the arterial blood and the decrement of pulmonary arterial pressure or change in pulmonary vascular resistance during the period of breathing oxygen.

DISCUSSION

Cardiac Output: The increased resting cardiac output during hypoxic states is a compensatory mechanism with which the tissue metabolic demands for oxygen are obtained. While the patient is breathing 99.6% oxygen,

the quantity of oxygen carried to the peripheral tissue per cubic centimeter of blood is increased; therefore, the quantity of blood needed to transport an optimal amount of metabolic oxygen is diminished. The data listed in table 2 pertaining to the increased flow of blood in the hypoxic state confirm the reports of Wiggers [6] and Harrison.[5]

It is known from the law of Poiseuille that in a nonrigid tube the resistance remains constant at different rates of flow if the tube length and radius and viscosity of the liquid remain constant. The partial correlation coefficients listed in table 4 indicate a closer relationship between decreased pulmonary vascular resistance and the increased percentage oxygen saturation of the blood than between changes of resistance and flow. It is concluded that the decreased resistance was mainly because of dilatation of the pulmonary arterioles in the group of patients studied.

Pulmonary Arterial Pressure: There is ample evidence [1, 2, 3, 21] to show that acute hypoxia leads to an elevation of the pulmonary arterial pressure. The exact mechanism of the effects of slowly developing hypoxia on the pulmonary vascular structures has not been clearly defined. In a state of prolonged hypoxia with increased vascular hypertonicity and increased pressure in the pulmonary artery, hypertrophy of the vascular walls occurs with thickening of the intima.[18] Therefore, instantaneous vascular resistance is magnified according to the law of Poiseuille as the radius of a tube diminishes, assuming flow, viscosity and length to be constant. In this series of patients there was close correlation between the change in flow, pulmonary arterial pressure, and the change in percentage oxygen saturation of the arterial blood when the effects of each on the other were analyzed with the partial correlation method of analysis (table 3).

Pulmonary Vascular Resistance: Pulmonary vascular resistance in this study includes the resistance to flow in (1) the pulmonary artery and its branches, (2) the capillary plexus, (3) the pulmonary veins. In a previous publication, Wilson and associates [10] presented evidence to show that the pulmonary arterial wedge pressure was not significantly different from the mean left atrial pressure. It was concluded that the dynamic pulmonary capillary pressure could not be measured with the present methods used during the procedure of right heart catheterization; therefore, pulmonary arteriolar resistance had never been calculated in man or dogs. However, anatomic studies alone would lead one to conclude that the point of greatest resistance to flow in the pulmonary vascular system is the pulmonary arteriolar and capillary plexuses. There has been disagreement regarding the mechanism of constriction and dilatation of the pulmonary arterioles. Histologically the necessary structures are present, namely, smooth muscle and a nerve supply for reactivity to stimuli as in the peripheral systemic arterioles. Stroud and associates [20] showed in dogs that pulmonary vascular constriction was reduced in magnitude under anesthesia. Dale and associates [22] observed the vasoconstrictor effect of stimulating either vagi or the stellate ganglion. This effect was eliminated by Nembutal anesthesia.

Woodbury [23] noted in dogs that the increased pulmonary arterial pressure following the injection of histamine was abolished by morphine and Nembutal. Rohn [21] concluded from his sympathectomy experiments that the pulmonary arterioles are under the active control of the sympathetic nervous system. The results of his experiments indicate that the vasoconstrictive response of the pulmonary vessels to hypoxia was of the same order of magnitude as that resulting from stimulation of the sympathetic nervous system. He concluded that pulmonary vasomotion resulting from alterations in the blood and alveolar oxygen tension is to some degree dependent upon the sympathetic innervations. On the other hand, Dirken and Hemstra [24] demonstrated in the rabbit that bilateral sympathectomy with removal of the sympathetic chain from the superior cervical ganglia down through the third thoracic had no effect upon the shunting of blood away from the nitrogen breathing lung. It may be that the effects of oxygen breathing at low tension are different in the rabbit from those in the dog.

The fundamental advantage of vasoconstriction to low oxygen tension in the alveoli is to redistribute blood to more adequately ventilated portions of the lung. In this manner the percentage oxygen saturation of the blood is maintained at a higher level in the presence of pathologic pulmonary tissue. In chronic hypoxic states this shunting mechanism with vascular constriction is continuous, and may lead to irreversible pulmonary vascular sclerosis.

Summary and Conclusions

1. The cardiac output in hypoxic patients with pulmonary emphysema is lowered when 99.6% oxygen is breathed.

2. The mean total pulmonary vascular resistance is decreased from 417.2 dynes cm sec^{-5} to 366.4 dynes cm sec^{-5} during the period of oxygen breathing.

3. The pulmonary arterial pressure decreases because of (1) the fall in cardiac output, and (2) the diminution of pulmonary vascular resistance.

4. Pulmonary arterial hypertension in patients with chronic pulmonary emphysema is not primarily due to hypoxia, but is caused by the loss of large areas of pulmonary alveolar tissue and capillary plexuses and sclerosis of the pulmonary arterioles, leading to a great diminution of the volume of the pulmonary vascular bed.

5. The mean pulmonary arterial wedge pressure decreased slightly but significantly from 5.16 mm. Hg to 4.03 mm. Hg during the period of breathing 99.6% oxygen.

BIBLIOGRAPHY

1. Von Euler, U. S., and Liljestrand, G.: Observations on the pulmonary arterial blood pressure in the cat, Acta physiol. Scandinav. **12**: 301, 1946.

2. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: The influence of short periods of induced acute anoxia upon pulmonary artery pressure in man, Am. J. Physiol. **150**: 315, 1947.

3. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J.: Anoxia and human pulmonary vascular resistance, J. Clin. Investigation **30**: 957, 1951.
4. Liljestrand, G.: Regulation of the pulmonary arterial blood pressure, Arch. Int. Med. **81**: 162, 1948.
5. Harrison, T. R.: Principles of internal medicine, 1st Ed., 1950, The Blakiston Co., Toronto, p. 138.
6. Wiggers, C. J., and Katz, L. N.: The static and dynamic effort of the heart during ejection, Am. J. Physiol. **85**: 229, 1928.
7. Ford, M. L., Petersly, C. L., Young, A. F., and Wiggers, C. J.: Effect of acute anoxia on the economy of effort index in man, Proc. Soc. Exper. Biol. and Med. **45**: 353, 1940.
8. Darling, R. C., Cournand, A., and Richards, D. W., Jr.: Studies on the intrapulmonary mixture of gases. III. An open circuit method for measuring residual air, J. Clin. Investigation **19**: 609, 1940.
9. Cournand, A., and Ranges, H. A.: Catheterization of the right auricle in man, Proc. Soc. Exper. Biol. and Med. **46**: 462, 1941.
10. Wilson, R. H., McKenna, W. T., Johnson, F. E., Jensen, N. K., and Mazzitello, W.: The significance of the pulmonary arterial wedge pressure, J. Lab. and Clin. Med. **42**: 408, 1953.
11. Haldane, J. S.: Methods of air analysis, 1912, Charles Griffin and Co., Ltd., London.
12. Wilson, R. H., Borden, C. W., and Ebert, R. V.: Adaptation to anoxia in chronic pulmonary emphysema, Arch. Int. Med. **88**: 581, 1951.
13. Dempsey, M. E., and Wilson, R. H.: Normal human oxygen saturation of the arterial blood as determined by gasometric analysis, J. Lab. and Clin. Med. **43**: 791–797 (May) 1954.
14. Wilson, R. H., and Ognanovich, J.: pH of whole arterial blood, J. Lab. and Clin. Med. **37**: 129, 1951.
15. Singer, R. B., and Hastings, A. B.: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood, Medicine **27**: 223, 1948.
16. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest, Am. Heart J. **41**: 30, 1951.
17. Fisher, R. A.: Statistical methods for research workers, 9th Ed., 1944, Oliver and Boyd, Ltd., Edinburgh.
18. Ljungdahl, M.: Untersuchungen ueber die Arteriosklerose des kleinen Kreislaufs, 1915, J. F. Bergmann, Wiesbaden, p. 196.
19. Issakssohn, von: Pathologisch-anatomische Veränderungen der Lungengefässe beim Emphysem, Virchows Arch. f. path. Anat. **53**: 466, 1871.
20. Stroud, R. C., and Rohn, H.: Effect of O_2 and CO_2 tensions upon the resistance of pulmonary blood vessels, Am. J. Physiol. **172**: 211, 1953.
21. Rohn, H., and Bahnson, H. T.: Effect of unilateral hypoxia on gas exchange and calculated pulmonary blood flow in each lung, J. Appl. Physiol. **6**: 105, 1953.
22. Dale, A. S., and Narayna, B.: Observations on the perfused lungs of the guinea pig, Quart. J. Exper. Physiol. **25**: 85, 1935.
23. Woodbury, R. A., and Hamilton, W. F.: The effect of histamine on the pulmonary blood pressure of various animals with and without anesthesia, J. Pharmacol. and Exper. Therap. **71**: 293, 1941.
24. Dirken, M. N. J., and Hemstra, H.: Alveolar oxygen tension and lung circulation, Quart. J. Exper. Physiol. **34**: 193, 1948.

GOLD–HORMONAL THERAPY IN RHEUMATOID ARTHRITIS *

By Paul J. Bilka, M.D., and Max H. Weil, M.D.,
Minneapolis, Minnesota

Since the introduction by Hench [1] of cortisone and corticotropin to clinical medicine, the value of these agents in certain acute disorders has been widely accepted. Their helpfulness and, at times, lifesaving nature are recognized. When they are administered for short periods the problem of "toxicity" or adverse physiologic effects of these hormones is minimal and is usually greatly overbalanced by their beneficial effects. However, in the treatment of a chronic disorder such as rheumatoid arthritis, where continued administration of the potent physiologic agent is required in order to maintain its benefits, the clinician is forced to ask himself the question: Am I likely to do more harm than good by using this drug?

The American Rheumatism Association is currently conducting a rather intensive study of long-term cortisone therapy in rheumatoid arthritis. Its data should be of great help in answering this question. Others are studying the use of cortisone, related steroids, and other drugs, in various combinations and "courses," in an attempt to reduce the necessity for prolonged cortisone therapy. Thus far these efforts have been unsuccessful.[2]

On the premise that it is generally desirable to limit the administration of cortisone to relatively short-term periods, especially in patients who require over 50 mg. per day for the adequate control of their symptoms, a study was begun in 1950 of combined gold-cortisone therapy in severe rheumatoid arthritis. The desire was to determine whether the combined use of these two anti-rheumatic drugs offered any advantage over the use of each alone. Of particular interest was the relapse rate following the cessation of cortisone and the continuation of gold. Chrysotherapy, it was postulated, might lessen the need of prolonged cortisone therapy in some patients.

Other Studies

Some disagreement exists concerning the place of gold in the treatment of rheumatoid arthritis, but most rheumatologists accept the evidence for its usefulness. Ragan,[3] although feeling that gold does influence the course of the disease in a significant percentage of patients, expresses doubt that the administration of gold has changed the natural history of the disease when viewed from the perspective of a five-year follow-up. In a review of the arguments for and against chrysotherapy, Hench states: [4] "The balance sheet shows that currently a patient so treated has about a 10 to 15 per cent

* Received for publication April 30, 1954.
From the Department of Medicine, University of Minnesota Medical School, Minneapolis.

chance of obtaining a 'complete remission' lasting several months to an undetermined number of years, about a 50 per cent additional chance of being notably improved, about a 35 per cent chance of obtaining no significant relief. On the other side of the ledger he has a 50 per cent chance of having no toxic reaction, a 45 per cent chance of having a minor or moderate reaction, a 3 to 5 per cent chance of a serious but nonfatal toxic reaction, and about 1 chance in 250 (0.4 per cent) of developing a fatal reaction." It is probable that with the use of BAL the serious and fatal categories of reaction can be considerably reduced. More optimistic results are reported with gold therapy in early rheumatoid arthritis.[5]

Margolis and Caplan [6] added the use of ACTH to the treatment of 10 patients who were on gold for their rheumatoid arthritis. One patient maintained a remission after the ACTH was discontinued. Thirteen patients were started simultaneously on ACTH and gold, and six maintained a remission after ACTH was discontinued. Although the follow-up period was rather short in some of these cases, and the authors presented their data as preliminary observations, these results are superior to those usually reported from the use of gold alone.

Thompson and Rowe [7] added cortisone to the treatment of eight patients who were only partially responsive to gold. Despite an excellent therapeutic response, no complete remissions were maintained. All patients returned to their pre-cortisone state shortly after the hormone was discontinued. Of 13 patients given gold concurrently with cortisone, two maintained a remission after the cortisone was discontinued. The authors conclude that combined therapy seemed to arrest rheumatoid arthritis in approximately the same percentage of patients as when gold was given alone. Only one toxic reaction to gold occurred, and the authors express the belief that patients who have previously been intolerant to gold can be given gold plus cortisone with less danger of a reaction to gold.

Coste et al.[8] treated 81 patients with gold and ACTH or cortisone. They report a 50% remission rate when gold is started before or at the same time as the hormone, but they state that treatment with gold is useless after hormone therapy. Some protective effect of the hormones on gold toxicity was described.

Some investigators [2, 9] report that combined gold-cortisone therapy has little or no value, and others [10] suggest that the individual benefits of each agent are lost if the two are given concurrently. In a discussion of the problem at the 1952 meeting of the American Rheumatism Association,[11] no agreement was reached on the place of combined gold-hormone therapy in rheumatoid arthritis.

Present Study

A total of 50 patients was given gold in combination with hormone therapy. Forty-one patients were given a minimum of 500 mg. of gold salt and were followed for at least three months after the cessation of hor-

mone therapy. These 41 cases constitute the basis for our conclusions concerning the effectiveness of combined gold-hormone treatment. Clinical details of these patients are included in table 1. Nine patients did not meet these minimal criteria (seven developed early toxic reactions, and two left the study before three months), and they are included only in the analysis of data concerning gold toxicity.

Aurothioglucose * was the soluble gold salt used in 38 patients; sodium aurothiomalate † was used in two patients, and the remaining patient received both preparations. The hormonal agent used was cortisone ‡ alone in 34 cases; hydrocortisone ‡ ("free" alcohol) in two cases; corticotropin

TABLE 1 *

Patient (Age-Sex)	Duration of Arthritis	Functional Impairment(13) Class†	Hormone Therapy (Amount and Duration)	Total Gold Salt at Cessation of Hormone	Present Therapy	Follow-up after Cessation of Hormone	Present Functional Class	Therapeutic Response(13) Grade‡
1. 27 M	1 yr.	III	2.5 gm. E in 6 wks.	235 mg. S	Gold	13 mos.	I	I
2. 29 F	2 mos.	III	3 gm. E in 2 mos.	730 mg. S	None	32 mos.	I	I
3. 69 F	1 yr.	III	6 gm. E in 3 mos.§	890 mg. S	None	12 mos.	I	I
4. 26 F	6 wks.	III	2.75 gm. E in 1 mo.	335 mg. S	None	34 mos.	I	I
5. 73 M	5 yrs.	III	2.275 gm. E in 1 mo.	960 mg. S**	None	39 mos.	I	I
6. 67 F	20 yrs.	IV	5 gm. E in 4½ mos.	885 mg. S	Gold	19 mos.	II	I
7. 46 M	9 mos.	III	6 gm. E in 4 mos.§	590 mg. S	None	13 mos.	I	I
8. 81 F	1 yr.	III	5 gm. E§ in 4 mos.	850 mg. S	E	18 mos.	II	II
9. 55 M	5 yrs.	III	8 gm. E§ in 4½ mos.	825 mg. S	None	14 mos.	I	II
10. 66 M	6 yrs.	IV	6 gm. E in 4 mos.	780 mg. S	Gold	12 mos.	II	II
11. 60 F	18 mos.	III	3.5 gm. E in 16 wks.	780 mg. S	Gold	10 mos.	I	II
12. 52 F	1 yr.	IV	2.4 gm. E plus 4.8 gm. F in 6 mos.§	930 mg. M	Gold	9 mos.	II	II
13. 72 F	7 yrs.	III	5.5 gm. E in 4½ mos.§	680 mg. S	Gold	24 mos.	I	II
14. 66 F	6 mos.	III	7 gm. E in 5½ mos.	1000 mg. S	None	8 mos.	I	II
15. 58 F	1 yr.	II	3.5 gm. E & F in 2 mos.§	35 mg. S	Gold	10 mos.	II	II
16. 35 F	2 yrs.	II	5 gm. E in 5 mos.	900 mg. S	Gold	3 mos.	I	II
17. 57 F	30 yrs.	IV	3 gm. E in 2 mos.	375 mg. M	Gold	17 mos.	III	II
18. 46 F	3 yrs.	III	7.5 gm. F in 6 mos.§	805 mg. S	Gold	5 mos.	I	II
19. 26 F	14 yrs.	III	ACTH for 3½ mos.§	740 mg. S	Gold	5 mos.	II	II
20. 54 F	8 yrs.	III	2 gm. E in 1 mo.	385 mg. S**	None	26 mos.	I	II
21. 50 F	10 yrs.	II	3 gm. E in 7 wks.	360 mg. S	Gold	3 mos.	I	II
22. 42 M	8 yrs.	II	3.35 gm. E in 3 mos.	700 mg. S**	None	23 mos.	I	II
23. 28 F	5 yrs.	IV	4 gm. E in 2½ mos.§	1500 mg. S	Gold	7½ mos.	I	II
24. 49 F	12 yrs.	IV	ACTH for 10 wks. (interrupted courses)§	1055 mg. S	None	3 mos.	III	III

* "Solganal," supplied through the courtesy of Schering Corporation.
† "Myochrysine," supplied through the courtesy of Merck and Co.
‡ Supplied through the courtesy of Merck and Co.

TABLE 1—*Continued*

Patient (Age-Sex)	Duration of Arthritis	Functional Impairment[13] Class†	Hormone Therapy (Amount and Duration)	Total Gold Salt at Cessation of Hormone	Present Therapy	Follow-up after Cessation of Hormone	Present Functional Class	Therapeutic Response[13] Grade‡
25. 50 F	8 yrs.	III	3 gm. E in 2½ mos.	450 mg. S	None	21 mos.	II	III
26. 59 F	6 yrs.	II	3.1 gm. E in 7 wks.	415 mg. S**	None	32 mos.	II	III
27. 38 F	8 yrs.	II	3 gm. F in 6 wks.	540 mg. S**	Gold	24 mos.	I	III
28. 63 F	40 yrs.	III	2.65 gm. E§ in 2 mos. (3 wks. off); 2.0 gm. E in 2 mos.	475 mg. S 875 mg. S	E***	27½ mos.	II***	III
29. 28 F	4 yrs.	III	5 gm. E in 3 mos.§	865 mg. S	F	33 mos.	II	IV
30. 54 M	6 mos.	III	1 gm. E in 3 wks.§	85 mg. S	None	22 mos.	III	IV
31. 30 F	6 yrs.	III	8 mos. E§	155 mg. S 550 mg. M	F	24 mos.	II	IV
32. 31 F	9 yrs.	II	4.5 gm. E in 4 mos.	815 mg. S	E plus gold	12 mos.	II	IV
33. 56 M	16 yrs.	II	2.75 gm. E in 1½ mos. (4 wks. off); 2.875 gm. E in 1½ mos.	470 mg. S 880 mg. S	E plus gold	30 mos.	II	IV
34. 62 M	11 yrs.	III	3 gm. E in 2½ mos.	510 mg. S**	None	18 mos.	II	IV
35. 55 F	2 yrs.	II	5 gm. E in 7 mos.§	915 mg. S	E	24 mos.	II	IV
36. 53 F	6 mos.	III	7 mos. E§	1230 mg. S	E	26 mos.	II	IV
37. 40 M	3½ yrs.	III	4.25 gm. E in 2 mos.§	375 mg. S	E	7 mos.	II	IV
38. 59 F	9 yrs.	III	2½ mos. ACTH plus E§	775 mg. S	E***	3 mos.	IV***	IV
39. 34 F	8 mos.	III	8 gm. E in 3½ mos.	535 mg. S	None	30 mos.	II	IV
40. 57 F	3 yrs.	III	3 gm. E in 1 mo.	1535 mg. S**	E	34 mos.	II	IV
41. 30 F	7 yrs.	IV	3.5 gm. E in 4 mos.	715 mg. S	E	24 mos.	IV	IV

* Abbreviations: E = cortisone; F = hydrocortisone; S = Solganal; M = Myochrysine.

† Class I = complete ability to carry on usual duties without handicap; Class II = adequate for normal activities; Class III = limited; Class IV = incapacitated: little or no selfcare.

‡ Grade I = complete remission; Grade II = major improvement; Grade III = minor improvement; Grade IV = no improvement.

§ Hormone started before gold.

** Gold started before hormone.

*** At time of death of unrelated disorder.

in two cases; cortisone and hydrocortisone in two cases, and cortisone plus corticotropin in one case. No significant difference attributable to these individual gold or hormonal preparations was noted.

Twenty-two patients had received no hormone prior to the start of gold, while 19 patients had had such prior hormonal therapy. Table 2 shows the therapeutic results (using the criteria of the American Rheumatism Association [12]) in the entire group and when the group is broken down according to the time of the onset of combined therapy. Coste [13] has stated that gold is ineffective when begun after hormones have been started. Although the proportion of complete remissions is lower in the prior hormone therapy group, we do not believe that the over-all results of the various groups are significantly different. A rather striking similarity is noticed in these results and those reported from the use of gold alone, and we

interpret the data as indicating that hormone therapy neither potentiates nor inhibits the effectiveness of gold.

It has been reported that cortisone tends to diminish, or even to eliminate, the risk of gold toxicity. Table 3 lists our experience with 50 patients. It is apparent that gold reactions can occur during hormone therapy; several occurred while patients were getting daily doses of 75 to 100 mg. of cortisone. Our maximal gold dosage was 50 mg. of the salt given once a week. It was noticed, however, that an uncommon number of reactions occurred

TABLE 2

Therapeutic Results

Grade[13] of Effectiveness	Total Group	Simultaneous Onset Gold Plus Hormone	Prior Gold with Addition of Hormone	Prior Hormone with Addition of Gold
I (Remission)	7 (17%)	4	1	2
II	16 (39%)	6	2	8
III	5 (12%)	1	2	2
IV (No change)	13 (32%)	4	2	7
	41 (100%)	15	7	19

soon after the cessation of the hormone. Of the 12 such reactions listed, nine occurred within the first month after hormone therapy was stopped. This raises the question of whether these hormones exert some suppressive effect on gold toxicity. It would appear that the physician should be alerted to extra caution during this post-withdrawal period.

Of the 23 patients with toxic gold reactions, 15 developed skin rashes, two developed skin and mouth lesions, one developed mouth lesions and diarrhea, one developed mouth lesions alone, three developed albuminuria,

TABLE 3

Gold Toxicity and Combined Therapy

Total Patients	No Toxic Reaction	Toxic Reaction While on Hormone	Toxic Reaction After Hormone Stopped
50	27 (54%)	11 (22%)	12 (24%)

and one developed leukopenia. In 17 patients the reaction was believed to be sufficiently severe to warrant discontinuance of gold therapy, but in none was it severe enough to require BAL or other special measures. The incidence and nature of these reactions do not appear to be notably different from those observed with gold alone.

SUMMARY AND CONCLUSIONS

Fifty patients with severe rheumatoid arthritis were given a combination of gold and cortisone, hydrocortisone or corticotropin. Forty-one patients

tolerated a minimum of 500 mg. of gold salt and were followed for at least three months.

Seventeen per cent of the patients maintained a complete remission of their disease; an additional 39% showed major improvement. Twelve per cent showed moderate improvement, and 32% maintained little or no improvement on gold after the hormone was stopped. These results closely approximate those obtained following the use of gold alone.

The incidence of gold reactions was 46%. In 34% gold was discontinued because of toxicity. Hormone therapy does not lessen the need for the usual precautions when gold salts are used.

Combined therapy offers a practical means of treating the severe active rheumatoid arthritic. Cortisone, hydrocortisone or corticotropin can be used to suppress the disease for several weeks to months while the gold depot is being built up. The hormone can then be discontinued with the expectation of obtaining the same therapeutic result as if gold alone were administered. Patients not showing a favorable response to the combined program can be treated by long-term maintenance on small doses of hormone, or by an intensification of the usual conservative measures of established value in the care of the patient with rheumatoid arthritis.

BIBLIOGRAPHY

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis, Proc. Staff Meet., Mayo Clin. **24**: 181–197 (Apr. 13) 1949.
2. Freyberg, R. H., Patterson, M., Adams, C. H., Durivage, J., and Traeger, C. H.: Practical considerations of the use of cortisone and ACTH in rheumatoid arthritis, Ann. Rheumat. Dis. **10**: 1–15 (Mar.) 1951.
3. Ragan, C.: Rheumatoid arthritis. The natural history of the disease and its management, Bull. New York Acad. Med. **27**: 63–74 (Feb.) 1951.
4. Editorial: Gold salts for rheumatoid arthritis, Ann. Int. Med. **26**: 618–624 (Apr.) 1947.
5. Adams, C. H., and Cecil, R. L.: Gold therapy in early rheumatoid arthritis, Ann. Int. Med. **33**: 163–173 (July) 1950.
6. Margolis, H. M., and Caplan, P. S.: The effects of pituitary adrenocorticotropic hormone (ACTH) in rheumatoid arthritis, J. A. M. A. **145**: 382–389 (Feb. 10) 1951.
7. Thompson, H. E., and Rowe, H. J.: Cortisone and gold therapy in chronic rheumatoid arthritis, Ann. Int. Med. **36**: 992–1000 (Apr.) 1952.
8. Coste, F., Caylee, J., Delbarre, F., and Piguet, B.: Chryso-hormonal association in chronic evolutive polyarthritis, Rev. rhumat. Par. **20**: 1, 1953.
9. Kammerer, W. L., Cecil, R. L., and Robbins, C.: Report at meeting of New York Rheumatism Association, April, 1952.
10. Batterman, R. C., Traeger, C. H., and Wainerde, H.: Report at meeting of New York Rheumatism Association, April, 1952.
11. Ensign, D. C., and Sigler, J. W.: Combination therapy in the treatment of rheumatoid arthritis, Ann. Rheumat. Dis. **11**: 306–308 (Dec.) 1952.
12. Steinbrocker, O., Traeger, C. H., and Batterman, R. C.: Therapeutic criteria in rheumatoid arthritis, J. A. M. A. **140**: 659–662 (June 25) 1949.
13. Coste, F.: Association Chryso-Hormonale, August, 1953, VIII[e] Congrès International des Maladies Rheumatismales, Genève, pp. 99–105.

APICAL DIASTOLIC MURMURS SIMULATING MITRAL STENOSIS. II. GRAPHIC DIFFERENTIATION *

By Aldo A. Luisada, M.D., F.A.C.P., † Olga M. Haring, M.D., ‡ and Ario B. Zilli, M.D., § *Chicago, Illinois*

It has been known for a long time that patients with a normal mitral orifice may present a low-pitched diastolic or presystolic murmur which is indistinguishable upon auscultation from that of mitral stenosis. Such a murmur has been described in aortic regurgitation,[1] pericardial or hypertensive heart disease,[2] rheumatic heart disease without mitral stenosis,[3, 4] and myocarditis.[5]

Later on, phonocardiographic studies gave objective evidence of the existence and subsequent disappearance of the murmurs. In some of the cases the murmur was documented during life by the tracing, and autopsy disclosed that no mitral stenosis existed. A group of 13 patients with rheumatic, hypertensive or coronary heart disease was reported by one of us with Montes in 1950.[6] In some of them the tracing demonstrated that the diagnosis of mitral stenosis was due to an auscultatory illusion (diastolic extra-sounds or crescendo-type of first heart sound) while, in the others, the tracings did not reveal the "functional" nature of the murmur and only the subsequent clinical course and additional tracings proved that there was no mitral stenosis.

Other graphic studies presented cases of patent ductus arteriosus,[7, 8] rheumatic or congenital heart disease,[10] cardiac cases of various etiologies,[11] and cases with an Austin Flint murmur.[12]

The present study was made in cases with an undeniable "functional" apical diastolic murmur. This investigation was instituted in order to find, if possible, graphic data which would permit a differentiation of these murmurs from those of organic mitral stenosis.

Material

The cases reviewed in this study were selected from the collection of the Division of Cardiology on the following basis:

1. They presented a low-pitched diastolic rumble, a presystolic murmur, or both.

* Received for publication August 27, 1954.

From the Division of Cardiology of The Chicago Medical School and The Mount Sinai Hospital of Chicago.

† Associate Professor of Medicine and Director, Division of Cardiology under a Teaching Grant of the U.S.P.H.S., National Heart Institute.

‡ Associate in Medicine and Research Associate under a Teaching Grant of the U.S.P.H.S., National Heart Institute.

§ Instructor in Medicine and Research Associate.

This study was aided by a grant of the Chicago Heart Association.

2. The "functional" nature of the murmur was demonstrated by (a) autopsy, (b) surgery, or (c) complete disappearance of the murmur following improvement in or cure of the clinical condition.

For each case a complete clinical, roentgenologic, and electrocardiographic study was made. The phonocardiogram was recorded, according to the routine procedure of the laboratory,[13] over five areas: apex, midprecordium, pulmonic, aortic and tricuspid areas. The tracings were recorded by means of a Sanborn stetho-cardiette (older tracings) or twin-beam (more recent tracings), first with a stethoscopic, then with a logarithmic device. In several cases "linear" tracings recorded the low frequency pulsations of the chest and the arterial pulse. In some of them electrokymograms of various cardiovascular structures were also recorded.

Results

Thirty-four cases were found corresponding to the various above described criteria. Nine had congenital heart disease; 16, acute rheumatic fever; six, coronary heart disease; four, syphilitic heart disease; one, severe anemia. (The total of 36 is greater than the actual number owing to overlapping of categories.)

Proof of the Functional Nature

The functional nature of the recorded murmur was proved as follows (table 1):

—by autopsy in 11 cases;

—by disappearance of the murmur following cardiovascular surgery (not on the mitral valve) in 2 cases;

Table 1

Etiology of Cases and Proof of Nature of Murmur

Etiology	Autopsy Findings No. of Cases	Disappearance after Surgery No. of Cases	Disappearance Following Clinical Improvement No. of Cases	Total
Congenital anomalies	6	2	—	8
Congenital anomalies plus rheumatic fever	—	—	1	1
Rheumatic fever	2	—	12	14
Rheumatic fever plus pregnancy	—	—	1	1
Coronary heart disease	1	—	2	3
Hypertensive and coronary heart disease	1	—	1	2
Coronary and syphilitic heart disease	1	—	—	1
Syphilitic heart disease	—	—	2	2
Syphilitic and hypertensive heart disease	—	—	1	1
Multiple myeloma and anemia	—	—	1 (blood transfusion)	1
Total	11	2	21	34

—by appearance of the murmur during observation, and its disappearance following clinical improvement (or only the latter) in 21 cases.

Spreading of the Murmur

The murmur was recorded over the following areas (table 2):
—apex and midprecordium, 19 cases
—apex and base, four cases
—entire precordium, 11 cases

Table 2

Graphic Characteristics of Murmurs in Relative Mitral Stenosis

Etiology	No. of Cases	Areas			Intensity				Distance between Beginning of QRS and Main Vibration of 1st Sound		Loud 3rd or 4th sd.
		Apex + Mid-prec.	Apex + Base	Entire Precordium	Less than 1st sd.	Between ½ and ⅔ of 1st sd.	Like 1st sd.	More than 1st sd.	More than 0.07	0.07 or less	
Congenital anomalies	9	5	1	3	3	4	2	—	1*	8	9
Acute rheumatic fever	15	11	—	4	3	8	4	—	1*	14	12
Coronary	3	1	1	1	—	2	—	1	—	3	3
Hypertensive and coronary	2	—	—	2	—	—	1	—	—	2	1
Coronary and syphilitic	1	—	1	—	—	—	—	1	1†	—	1
Syphilitic	2	1	1	—	2	—	—	—	2†	—	2
Hypertensive and syphilitic	1	1	—	—	—	—	1	—	1†	—	1
Multiple myeloma and anemia	1	—	—	1	—	1	—	—	—	1	—
Total	34	19	4	11	8	15	8	3	6	28	30

* QRS prolonged by B.B.B.
† QRS prolonged by left ventricular hypertrophy.

Intensity of the Murmur

In general, the vibrations of the murmur were of large amplitude. The intensity of the murmur was as follows (table 2):

(a) Two thirds of the first sound or less, 23 cases.
(b) Like the first sound, eight cases.
(c) Louder than the first sound, three cases.

The loudest murmurs were recorded in cases of coronary heart disease, the next loudest in syphilitic heart disease. However, four out of 14 cases of acute rheumatic fever also had a murmur with vibrations as high as those of the first sound.

Phase And Characteristics Of The Murmur

The murmur was early-diastolic in four cases, mid-diastolic in 19 cases (figures 1, 2, 3A, 4B), and presystolic in 22 cases (figures 4A, 5A, and 6). (Some cases had both a presystolic and a mid-diastolic murmur.)

The congenital cases presented a high percentage of presystolic murmurs (eight out of nine cases), and a good percentage of early-diastolic murmurs (four out of nine cases). The patients with coronary, syphilitic or hyper-

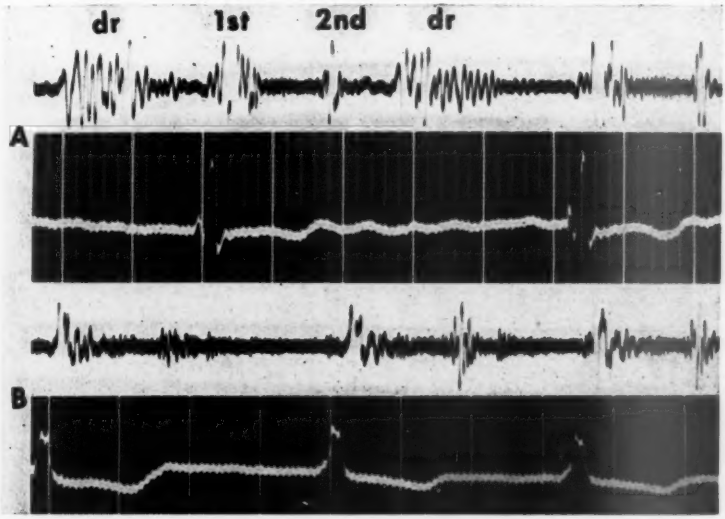

Fig. 1. Hypertensive and coronary heart disease. Possible luetic heart disease. Aortic insufficiency. Loud diastolic rumble (dr) at apex (A) which disappeared one year later (B).

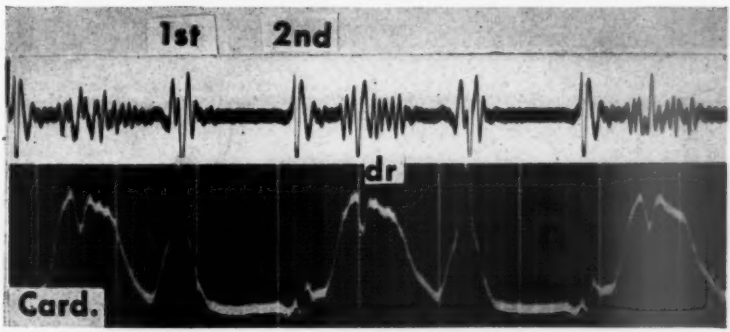

Fig. 2. Case of adhesive pericarditis. Diastolic rumble (dr) and diastolic thrust at midprecordium. Phonocardiogram and apex cardiogram (Card.).

tensive heart disease also often had a presystolic murmur (seven out of nine cases) and frequently a mid-diastolic murmur (five out of nine cases). The patients with acute rheumatic fever had the highest percentage of mid-diastolic murmurs (14 out of 16 cases) and the lowest percentage of presystolic murmurs (seven out of 16 cases).

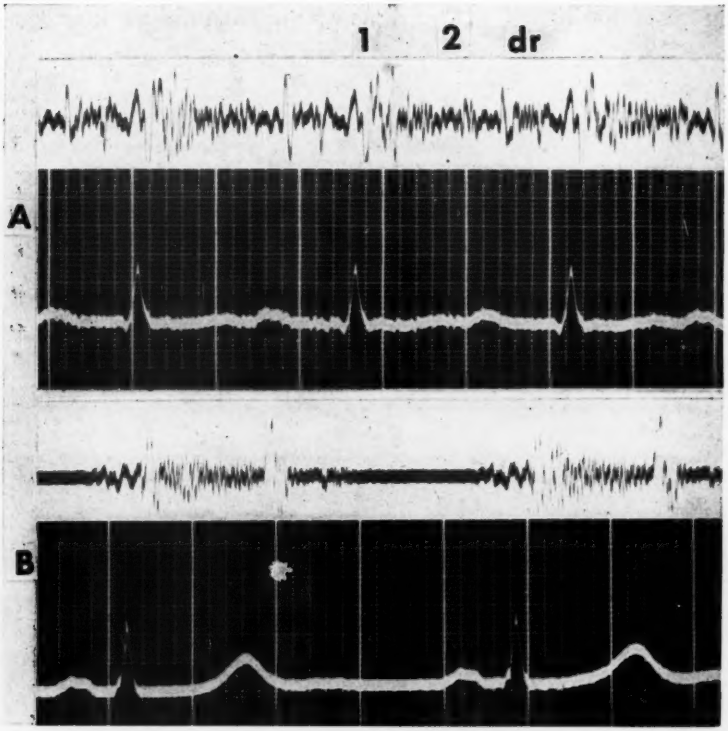

FIG. 3. Rheumatic heart disease with mitral regurgitation. A diastolic rumble (dr) appeared during an episode of acute carditis (A). It had nearly disappeared two months later (B).

In all cases the diastolic murmur started at a distance of more than 0.15 second from the second sound. In none of the cases was an opening snap of the mitral valve recorded at the apex or midprecordium. The first heart sound was never more than 0.07 from the beginning of QRS, except in cases with bundle branch block (table 2). A loud third or fourth sound was recorded in 30 out of 34 cases. Whenever the third sound was present, the vibrations of the murmur started immediately after it, so that both seemed part of the same phenomenon.

Discussion

The graphic characteristics of the diastolic murmur of mitral stenosis are the following:[13]

(a) In a large percentage of cases a pause follows the second sound. After the pause, which lasts from 0.08 to 0.11 second, a vibration occurs,

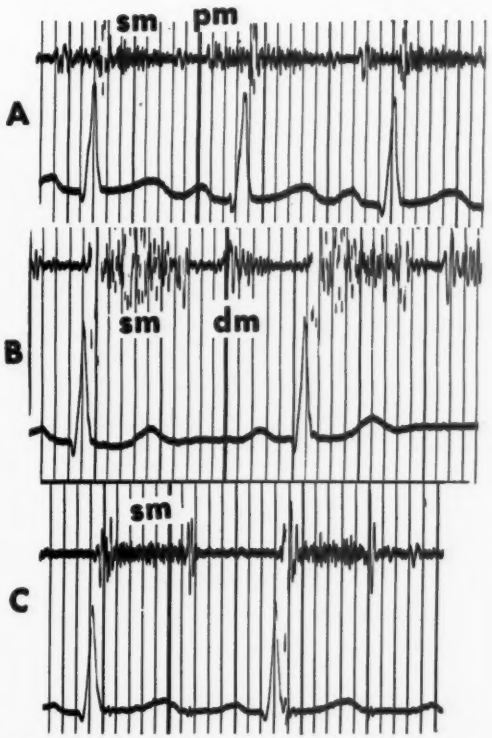

Fig. 4. Acute rheumatic carditis. (A) Presystolic (pm) and systolic (sm) murmurs. (B) One month later: diastolic rumble (dm) initiated by a loud third sound. (C) Four months later: following clinical improvement, only a low grade systolic murmur (sm) was present.

the opening snap of the mitral valve. This vibration (which may be the only sign of stenosis) marks the beginning of the murmur.

(b) The murmur is usually of low amplitude and presents irregular vibrations. It may have a greater amplitude at the time of rapid filling, and may even show a large vibration within the murmur (third sound), though such an event indicates a minor degree of stenosis. The murmur usually fades out toward mid-diastole if diastole is long, while it fuses with the presystolic murmur if diastole is short and sinus rhythm is preserved.

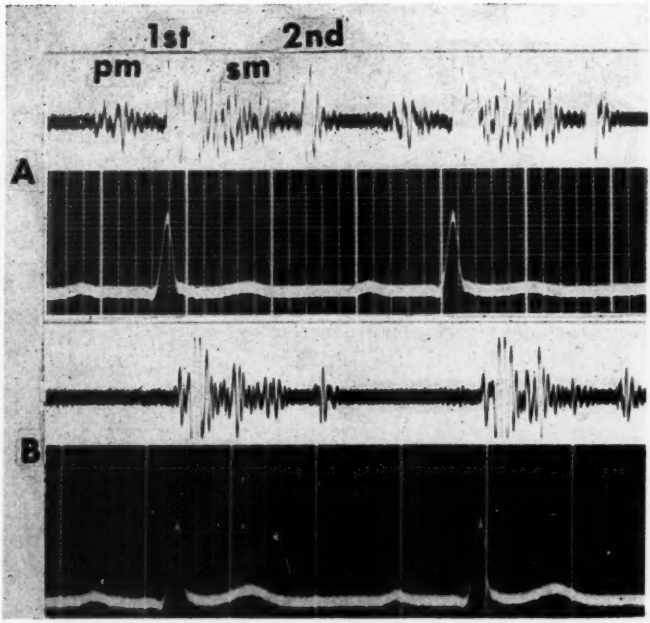

FIG. 5. Case of multiple myeloma with anemia. (A) Loud systolic (sm) and presystolic (pm) murmurs. (B) Following blood transfusion, the presystolic murmur had disappeared.

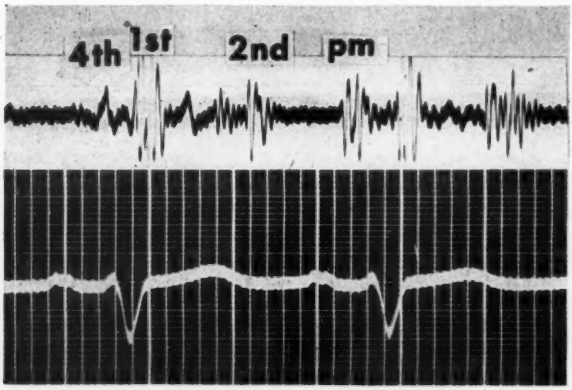

FIG. 6. Case of congenital heart disease (coarctation of the aorta plus patency of the ductus). Apical tracing. The first cycle shows a fourth (atrial) sound in presystole, while the second cycle has a presystolic murmur. No mitral stenosis at autopsy.

(c) In general, if sinus rhythm is present, there is a distinct presystolic murmur. This starts before the Q wave of the electrocardiogram and continues until the loud vibrations of the first sound. It usually has the type of murmur "in crescendo," but occasionally may be separated from the first sound if the conduction time is prolonged.

(d) The main vibrations of the first sound are delayed over the beginning of systole [14, 15] and start more than 0.07 second after the beginning of QRS.[16]

While the opening snap can be recorded over a wide area of the precordium, the diastolic and presystolic murmurs are usually recorded only within a limited area: at the apex, above the apex, or at the midprecordium.

TABLE 3

Differences Between Murmurs Due to Organic Mitral Stenosis and Relative Mitral Stenosis

	Organic Mitral Stenosis	Relative Mitral Stenosis
Opening snap	Frequently present	Absent (all cases)
Murmur starts	Between 0.08 and 0.11 second after second sound	More than 0.15 second after second sound (all cases)
Vibrations of murmur	Frequently of low amplitude	Usually loud (like first sound or louder in 30% of cases; from ½ to ⅔ of first sound in 44% of the cases)
Existence of third sound	Occasional	Nearly always present (30 out of 34 cases)
Area of registration	Usually limited	Often over all precordium (30% of cases); spread to base in some cases; rather large area beyond apex (60% of cases)
Delay of first sound over beginning of QRS	More than 0.07	No delay

Table 3 shows the differences between sound characteristics encountered in organic mitral stenosis and those encountered in relative mitral stenosis. They are both positive and negative.

I. *Positive qualities found in relative mitral stenosis*

(a) *The murmur is frequently loud* (figures 1, 2, 4). It is like the first sound or louder in 30% of the cases; from one-half to two thirds of the first sound in 44% of the cases. It should be noted that the lower amplitude is more frequently found in presystolic murmurs (four out of seven) for obvious reasons (shorter phase).

(b) *It is often recorded over a wide area* (all precordium in 30% of the cases; spreading to the base in some cases; over a wide area beyond the apex, in the others). *The murmur always starts more than 0.15 sec. after the second sound* (figures 1, 2, 4) in contrast to cases of organic mitral

stenosis. *A third sound is nearly always present* (30 out of 34 cases) (figures 1, 2, 4) in contrast to the rare occurrence of this sound in organic mitral stenosis.

II. *Negative qualities found in relative mitral stenosis.*

(a) There is *no opening snap* of the mitral valve. (This snap is frequent in organic mitral stenosis.)

(b) The main vibration of the first sound has *a normal relationship with the beginning of QRS* of the electrocardiogram (0.06 to 0.07). In organic mitral stenosis there is a constant delay [15, 16] which may increase in cases with severe arrhythmia due to atrial fibrillation.[14, 15]

The explanation for the murmur of these cases still seems to be that previously advocated by White [2] and by one of the authors,[6] namely, that of a *relative stenosis* of the mitral valve (disproportion between normal mitral

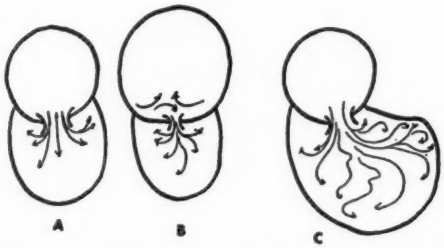

FIG. 7. Mechanism of production of a functional diastolic rumble at the apex. (A) Normal mitral valve. (B) Organic mitral stenosis. (C) Relative stenosis due to left ventricular enlargement.

ostium and large left ventricle, creating eddies within the ventricle) (figure 7). The large area of recording can be explained by the large area of contact of the left ventricle (coronary and hypertensive cases) or of both ventricles (acute carditis) with the precordium. In the latter cases, *relative stenosis of both the mitral and the tricuspid valves* is likely.

It should be noted that some of the graphic characteristics, and in particular the amplitude of the murmur, can be recognized best on a "stethoscopic" tracing which does not distort the picture by increasing the high-pitched vibrations. Therefore, records taken with a "logarithmic" method, like those of Wells,[16] may not be significant for the differentiation.

SUMMARY AND CONCLUSION

1. A study of the graphic characteristics of apical murmurs simulating those of mitral stenosis was made in 34 cases. The "functional" nature of the murmur was proved by autopsy in 11 cases, by disappearance following surgery (not on the mitral valve) in two cases, and by appearance of

the murmur during observation and subsequent disappearance following improvement in 21 cases.

2. Certain positive data were found helpful in recognizing the nature of the murmur: the murmur is frequently loud and occurs later in diastole; it is often recorded over a large area of the chest; there frequently is a third sound.

3. Certain negative data were also found helpful: there is no opening snap; the main vibration of the first sound has a normal relationship with the QRS complex.

4. The mechanism of production of the murmur is discussed.

5. Graphic data permit one to recognize the "functional" nature of the murmur in a great majority of the cases.

ACKNOWLEDGMENT

Acknowledgment is given to the staff of the Division of Cardiology and, in particular, to Dr. S. Contro, formerly associated with this institution, for their collaboration.

BIBLIOGRAPHY

1. Flint, A.: On cardiac murmurs, Am. J. M. Sc. **44**: 29, 1862.
2. White, P. D.: A note on the differentiation of the diastolic murmurs of aortic regurgitation and mitral stenosis, Boston M. and S. J. **195**: 1146, 1926.
3. Bland, E. F., Duckett Jones, T., and White, P. D.: The development of mitral stenosis in young people with a discussion of the frequent misinterpretation of a mid-diastolic murmur at the cardiac apex, Am. Heart J. **9**: 995, 1935.
4. Gibson, S.: Eyes, hands, and ears in the diagnosis of heart disease in children, Pediat. Clin. North America, p. 3 (Feb.) 1954.
5. Weinstein, M., and Lev, M.: Apical diastolic murmurs without mitral stenosis, Am. Heart J. **23**: 809, 1942.
6. Luisada, A. A., and Perez Montes, L.: A phonocardiographic study of apical diastolic murmurs simulating those of mitral stenosis, Ann. Int. Med. **33**: 56, 1950.
7. Ravin, A., and Darley, W.: Apical diastolic murmur in patent ductus arteriosus, Ann. Int. Med. **37**: 903, 1950.
8. Fishleder, B. L., and Medrano, G. A.: Retumbo apical en conducto arterial, Arch. Inst. cardiol. México **22**: 292, 1952.
9. Alimurung, M. M., Rappaport, M. B., and Sprague, H. B.: Variations in first apical sound simulating so-called "presystolic" murmur of mitral stenosis: phonocardiographic study, New England J. Med. **241**: 631, 1949.
10. Nadas, A. S., and Alimurung, M. M.: Apical diastolic murmurs in congenital heart disease, Am. Heart J. **43**: 691, 1952.
11. Luisada, A. A.: Functional diastolic murmurs at the apex simulating mitral stenosis, Proc. Inst. Med. Chicago **19**: 70, 1952.
12. Currens, J. H., Thompson, W. B., Rappaport, M. B., and Sprague, H. B.: Clinical and phonocardiographic observations on the Flint murmur, New England J. Med. **248**: 583, 1953.
13. Luisada, A. A.: The heart beat, 1953, P. B. Hoeber, New York.
14. Luisada, A. A.: Variable interval between electric and acoustic phenomena in atrial fibrillation, Am. Heart J. **22**: 245, 1941.
15. Cossio, P., and Berconsky, I.: El primer ruido cardiaco y el soplo presistolico en la estrechez mitral con fibrilacion auricular, Rev. argent. de cardiol. **10**: 162, 1943.
16. Wells, B. G.: The graphic configuration of apical diastolic murmurs, Brit. Heart J. **14**: 261, 1952.

PERICARDIAL CALCIFICATION AND HISTOPLASMIN SENSITIVITY *

By F. T. Billings, Jr., M.D., F.A.C.P., and O. A. Couch, Jr., M.D.,
Nashville, Tennessee

The cause of calcification of the pericardium in many instances is obscure. Agreement can be reached regarding etiology only in the statement that "calcification occurs as a secondary degenerative change complicating chronic inflammation of the pericardium." [1] In the majority of cases, by the time bacteriologic and pathologic studies can be undertaken, evidence of specific infection or injury is not demonstrable. It is intriguing to note that whenever disease entities are implicated, authorities are dogmatic in their differences of opinion. For example, while Paul, Castleman and White [2] in Boston found no evidence which would incriminate rheumatic fever, Smith and Willius [3] in Minnesota believed rheumatic fever to be the most common precursor. On the other hand, in Baltimore, Nashville and England pericardial calcification has been blamed chiefly on forerunning tuberculous pericarditis.[4, 5, 6] Suffice it to say that, although calcified pericardium frequently is due to tuberculous infection, pneumococcus and other purulent bacterial infections, rheumatic fever and trauma, in the majority of cases in many series reported the causative factor has remained unknown.[2, 7, 8]

It is appropriate that the suggestion of another cause of pericardial calcification, namely, histoplasmosis, should come from Vanderbilt, where the fungus etiology of the disease was first demonstrated.[9] The histories and other data regarding two patients are herewith presented. Neither patient had symptoms or signs related to the chance roentgenologic demonstration of calcium in the pericardium. Both had negative tuberculin and strongly positive histoplasmin skin tests.

Case Reports

Case 1. A 28 year old white insurance adjuster was first seen at home January 5, 1953, with a three day history of malaise, generalized aching and fever of 102° F. He had had a cold, had been overworked and felt very tired.

He had always been in general good health. There was no history of rheumatic fever, pneumonia or any unusual childhood illness. He had served in the Infantry during World War II in Mississippi, Kentucky, England and France. His health was good during military service. In 1946 he had a febrile illness which lasted two weeks, with temperature at times of 105° F. and symptoms of generalized aching, a feeling of stiffness and chilly sensations. He was given penicillin every four hours for five or six days and gradually improved. During this illness there was no sore throat, cough, chest pain or shortness of breath.

* Received for publication September 11, 1954.
From the Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee.
Aided in part by the John B. Howe Medical Research Fund.

Physical examination revealed no abnormality except for fever and a few small cervical lymph nodes and one small node in the right axilla. Laboratory investigations associated with this acute febrile illness were not specifically revealing except that the leukocyte count remained normal, with slight predominance of lymphocytes. The heterophil antibody titer reached a strength of 1:56. The temperature gradually subsided over a four week period without apparent response to several antibiotics. It is believed he may have had infectious mononucleosis.

FIG. 1. *Case 1.* Portion of roentgenogram showing thin curved line of calcium in pericardium at left cardiophrenic angle.

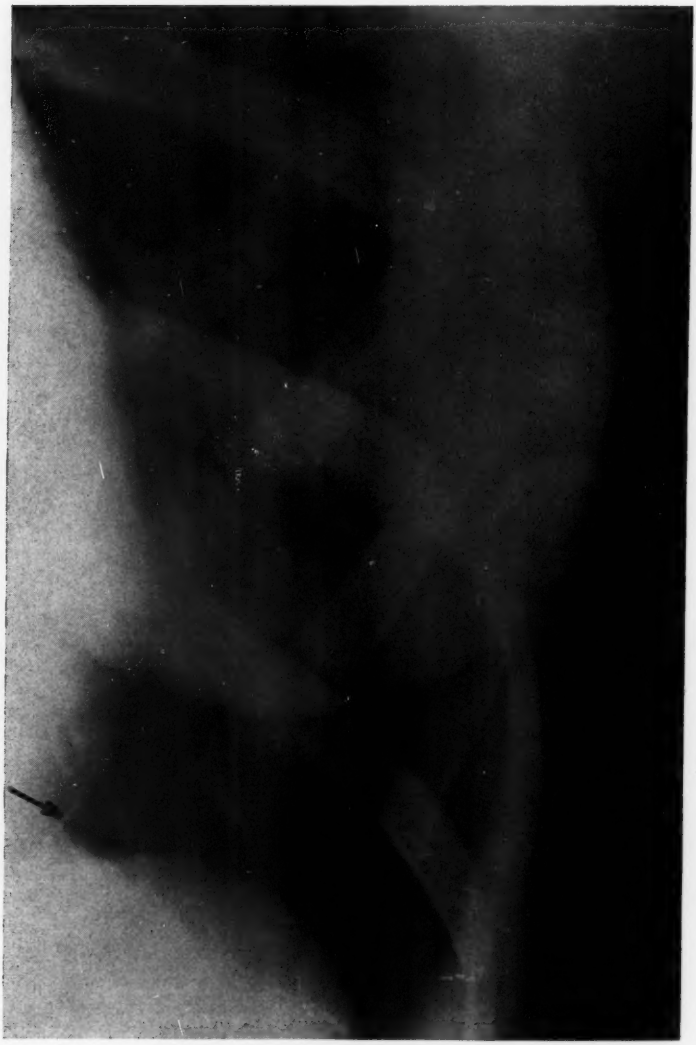

FIG. 2. *Case 2.* Portion of roentgenogram showing thin curved line of calcium in pericardium at left cardiophrenic angle.

Of special interest was the x-ray examination of the heart and lungs. On January 12, 1953, Dr. M. D. Ingram, Jr., reported: "The cardiac configuration is within normal limits. At the very apex of the heart there is a semi-circinate shadow of calcium. This is thought to be calcification of the pericardium in this area. Fluoroscopic examination of the heart reveals free movement of the cardiac shadow and confirms the presence of calcium in the pericardium" (figure 1).

The following intradermal skin tests were carried out, with results as indicated: two strengths of tuberculin (purified protein derivative, 0.00002 mg. and 0.005 mg., respectively, in 0.1 c.c.) were introduced intracutaneously, with no reaction after 48 hours. Coccidioidin skin test was negative. Histoplasmin, 1.0 mg. injected intracutaneously, produced a very strong positive reaction. There was an area of induration and erythema of approximately 8 by 14 cm. The center of this area was bluish red. A tuberculin patch test was negative.

Case 2. A 26 year old white housewife was admitted to Vanderbilt University Hospital April 12, 1954, with a very large number of nonspecific complaints. She had considered herself healthy until two years before her admission. At that time she had noted the gradual onset of trembly nervousness associated with palpitation and "thumping" of her heart, a feeling of weakness and inability to get a deep breath. She noted widespread, intermittent, rather transient aching and shooting pains in the front and back of her head, around her neck and shoulders and below her breasts. She had no appetite and in two years she lost 10 pounds. She tired easily, could never relax and, in her own words, "If I don't hurt one place I hurt another." At times she thought she had a fever but this was never confirmed, although for weeks at a time she kept regular temperature charts. She was referred for hospitalization in an effort to arrive at an explanation of her symptoms.

Her past had not been particularly eventful. She had always been nervous and highstrung. There had been no serious febrile illnesses, and there was no known history of rheumatic fever or pneumonia. The menstrual history was normal. Her husband, to whom she had been married seven years, was healthy, as was her four year old child.

The physical examination revealed no abnormality. She was thin (weight, 95 pounds; height, 64½ inches), and normally developed. Her blood pressure was 130–145/70–80 mm. of Hg. The rate and rhythm of the pulse, and the rectal temperature were consistently normal. No enlarged lymph nodes were present. The examination of the heart and lungs revealed no abnormality. The abdomen was flat and soft, and there was no tenderness. The liver and spleen were not enlarged. The pelvic organs were normal.

Laboratory investigations revealed a normal sedimentation rate and leukocyte count and no anemia. The differential white cell count was normal, as was the electrocardiogram. X-ray examination of the heart and lungs disclosed a thin, curvilinear shell of calcium in the pericardium at the left cardiophrenic angle (figure 2), and another streak in the pericardium just below the segment of the pulmonary artery on the left. Fluoroscopic visualization confirmed these findings. No limitation of free movement of the heart was observed. Old tuberculin, 0.01 mg. and later 0.1 mg., injected intradermally, produced no reaction. Histoplasmin, 0.1 mg. injected intradermally, produced a strong positive reaction.

Christie [10] has beautifully catalogued and impressively emphasized the protean nature of human histoplasmosis. He has shown that it is frequently very difficult to differentiate this disease from many others without histoplasmin skin testing. The histories of the two patients presented here give no clue as to the cause of the deposition of calcium in the pericardium. The strongly positive histoplasmin skin tests are findings which may or may not be related to this calcification. Histoplasmosis is suggested chiefly to stimulate further interest in this disease as another cause of calcified pericardium and perhaps even of constrictive pericarditis.

Summary

Two histories are presented of patients with roentgenologically demonstrated calcification of the pericardium, with negative tuberculin and positive histoplasmin skin tests. It is suggested that histoplasmosis may be another cause of calcification of the pericardium.

BIBLIOGRAPHY

1. Friedberg, C. K.: Diseases of the heart, 1950, W. B. Saunders and Co., Philadelphia, p. 539.
2. Paul, O., Castleman, B., and White, P. D.: Chronic constrictive pericarditis; a study of 53 cases, Am. J. M. Sc. **216**: 361, 1948.
3. Smith, H. L., and Willius, F. A.: Pericarditis. II. Calcification of the pericardium, Arch. Int. Med. **50**: 184, 1932.
4. Harvey, A. M., and Whitehill, M. R.: Tuberculous pericarditis, Medicine **16**: 45, 1937.
5. Blalock, A., and Burwell, C. S.: Chronic pericardial disease. Report of 28 cases of constrictive pericarditis, Surg., Gynec. and Obst. **73**: 433, 1941.
6. Andrews, G. S. W., Pickering, G. W., and Sellors, T. H.: The aetiology of constrictive pericarditis, with special reference to tuberculous pericarditis together with a note on polyserositis, Quart. J. Med. **17**: 291, 1948.
7. Rummert, O.: Über Perikardverkalkungen, Fortschr. Röntgenstrahl. **55**: 241, 1937.
8. Leaman, W. G., and Vastine, J. H., 2nd: Calcification of the pericardium. Report of a case in a boy aged 12, Am. J. Roentgenol. **43**: 35, 1940.
9. DeMonbreun, W. A.: The cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, Am. J. Trop. Med. **14**: 93, 1934.
10. Christie, A.: The disease spectrum of human histoplasmosis, T. A. Am. Physicians **64**: 147, 1951.

THE UTILIZATION OF PSYCHIATRIC MARGINAL MANPOWER IN MILITARY SERVICE *

By E. L. CAVENY,† Captain, (MC) USN, F.A.C.P., *Washington, D. C.*

IN recent years we have been hearing more and more about the broad and important subject of mental health. Lay and professional people are waking up to the realization of its tremendous implications. Most assuredly, it is a subject that has wide ramifications and in varying degrees affects all social and working groups—schools and teachers, churches and ministers, states and legislators, the armed forces and military personnel, medicine and physicians. In this ever-increasing problem, the burden as well as the guidance will continue to be that of the medical profession: the general practitioner and the psychiatrist alike.

Today's subject matter, that of individuals who are substandard and marginal from a psychiatric point of view, is but a segment of the large problem of mental health. It increases in importance simultaneously with manpower shortage. Confronted with manpower shortage, whatever the cause, it becomes necessary to utilize marginal personnel in both military and civilian mobilization. In this present highly technical and specialized age, not only is there an increased number of marginal individuals by virtue of the fact that intellectual demands are greater, but also their presence in any working group is far more disrupting and disturbing to the total functioning than it was a few decades back. Apparently the most satisfactory long-term solution to the problem of military and civilian manpower is the establishment of a sound, nation-wide program for the improvement of mental health and literacy in the over-all population, thereby lessening the number of marginal individuals within the manpower pool.

Prior to World War II little interest was shown in the selection, placement and utilization of physically and psychiatrically marginal manpower. In fact, the objective then was to exclude all men from both civilian employment and the military service who were in any way disabled, or who might become a casualty, psychiatric or otherwise. During World War II the shortage of manpower became generally acute. This stimulated various inquiries and experiments in the feasibility of utilizing certain physically handicapped and substandard personnel. As a result, specialized services were established to deal with the placing of individuals in employment and to follow up their performance to assure satisfactory job placement as to ability and efficiency. These services were soon discontinued as too in-

* Presented as a Morning Lecture at the Annual Session of The American College of Physicians, Chicago, Illinois, April 7, 1954.

The opinions expressed are those of the author and do not necessarily represent the opinions or policies of the Navy Department.

† Present address: Medical College of Alabama, Birmingham 5, Ala.

volved and not worth the effort. From these earlier experiments, however, the few studies that were undertaken revealed that the use of handicapped manpower was possible, and that in time there would be a statistical basis on which to determine whether the added expenditures involved in the utilization of any particular group of marginal individuals were warranted.[1]

The physically handicapped are not so frequently used in civilian employment and the military service as are the psychiatrically handicapped. This is due to the fact that the psychiatric impairments are not so readily determined, and become evident only over a period of observation on the job. While each is equally disabling, the psychiatric disability is likely to be more damaging to the group in that it frequently remains hidden as well as less acceptable. The extent to which psychiatric disabilities may be concealed is well indicated by a study[2] published in 1947, where an extensive investigation revealed that in a sample of 3,000 factory workers, between one fourth and one third of all sickness was due to neurosis.

During the past few years the Neuropsychiatry Branch of the Bureau of Medicine and Surgery has been engaged in an elaborate research program in which many thousands of methodized, objective records of service personnel have been scientifically studied and evaluated. Many factors have been clearly and conclusively revealed: (1) The desirable objective of excluding from the military service all men who might become a psychiatric casualty can be done only by excluding too great a segment of manpower resources. (2) In determining success or breakdown in military personnel, much greater emphasis is to be placed, over and above personality factors, on the stresses and supports of the environment in which the individual finds himself, and not so much emphasis on the application of clinical concepts to matters of military service, or to attempts at paralleling conditions in civilian and military life. (3) The utilization of the marginal group is not only feasible but also a necessity when the exigencies of the situation, as in time of war, bring about a manpower shortage. (4) A "selecting-in" program of service personnel is more desirable and effective than a "screening-out" program. (5) The presence of marginal individuals greatly increases the incidence of hospitalization and disciplinary difficulties, even though the group adjustmental standards are still met. (6) There are "hidden" and greater costs in providing for the additional demands made by this group on the medical, disciplinary and training facilities. (7) Statistics are being rapidly compiled which furnish a framework of reference for determining the feasibility of expenditure in the utilization of certain types of marginal manpower and ascertaining under what conditions, or where to draw the line with respect to using the handicapped. And, foremost, (8) research in this area must be a continuous process if the military services are effectively to utilize substandard personnel in the years to come. It is these data from such investigations that will be presented here.

Obviously, the psychiatric screening undertaken at Induction Stations in World War II was generally unsatisfactory. About 1,000;000 men were

rejected for military service because of psychiatric defects, and an additional 1,000,000 men were separated during their military service because of psychiatric conditions. Still, the psychiatric incidence rate in the military service during that war reached an all-time high. From the viewpoint of manpower this is truly wasteful. It is to be remembered that the cost of a psychiatric casualty in World War II has been fairly accurately estimated at $30,000. Recent studies [3, 4, 5] have rather conclusively indicated that a large percentage of the individuals rejected for psychiatric reasons probably could have served satisfactorily, while other studies [5] concluded that a large number of those who were discharged from the service during the war probably could have remained successfully.

The desirable objective of excluding all men from the military service who might later become a casualty is regarded as too costly with respect to manpower resources. Recently, samplings of an equal number of several thousand recruits who entered the Navy in the spring of 1943 were gathered from the three main training centers, and their subsequent service for the next three years was studied.[6] During that time the discharge rate for psychiatric reasons was as follows:

TABLE 1

Relation of Training Station Screening Rate to Subsequent Neuropsychiatric Attrition

Training Station	No.	% Discharged during Training	% Discharged Subsequently
Great Lakes	1525	4.5	1.5
Newport	1173	2.6	1.8
Sampson	2823	0.7	3.0

In this study the recruit bodies were of equal caliber, and were handled under the same selection procedures and by professional staffs of equal ability. The discharge rates differed, however, primarily because discharge at the recruit training center levels is a line command function. At that time the line command at the Great Lakes Center gave the psychiatric unit a free hand in controlling the rate of discharge for unsuitability, while the line command at the Sampson Center allowed a minimum to be discharged. This created, fortuitously, a setting lending itself to a perfect research situation. The results are shown here. The conclusions of this study emphasize first that, if psychiatric selection is valid, the more men selected-out during the training period the less psychiatric attrition there will be during subsequent military life. It is noted that there is an exact inverse ratio, with the Great Lakes group losing only 1.5 per cent and the Sampson group losing 3.0 per cent. Second, there is an optimal point beyond which increasing severity of selection does not yield comparable results. While the Great Lakes Center discharged nearly twice as many as Newport, the subsequent attrition rates were essentially the same.

When manpower shortage necessitates the lowering of physical and

mental standards of the military service, resulting in the utilization of marginal individuals, the repercussion is rapidly felt throughout. This is most significant regarding the situation with respect to the hospitalization rate for psychiatric illness. During the depression years of 1936 through 1940 the military services had a very high degree of selectivity as to both intellectual and physical standards. The period 1947 through 1949 continued as inflation years, and the rewards in civilian life and from the G. I. Bill of Rights rendered military employment undesirable.

Today, in the utilization of the marginal group the emphasis is on finding a method not only of "screening-out" more effectively and less wastefully individuals most likely to become casualties, but also of "selecting-in"

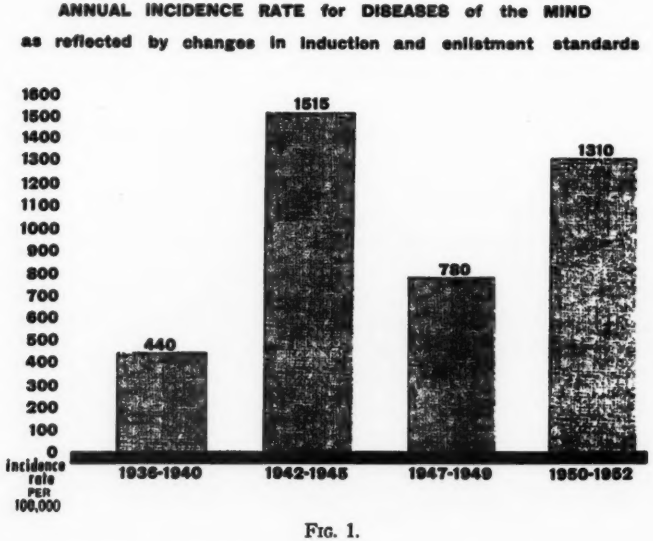

FIG. 1.

all individuals into a type of assignment whereby adjustment is more readily and firmly facilitated, and with the highest degree of efficiency. This "selecting-in" process is undertaken at training centers where the incoming recruit spends the first several weeks of his military life. It is in this setting and while on a duty status that the individual is observed as to behavior and performance. If he does not measure up to accepted standards, and a satisfactory assignment on limited duty seems out of the question, disposition is then accomplished on something more than a "guess." Over and above the personality structure, the effects of the various stresses and supports of the environment at this particular stage are paramount in determining the future success or breakdown of military personnel. Here again, studies [5] have revealed that there should be less emphasis on attempts at

paralleling conditions and clinical concepts in civilian and military life. If all recruits were studied over a given period of time as to the discharge and the length of service rates, the results would be quite similar to those of a study [5] made of all discharges during the month of August, 1952:

The majority of the individuals with physical defects are discovered and eliminated within the first few days. Psychiatric-wise, essentially all individuals are placed on duty and it is then, from observation of behavior and performance in their newly acquired environment, that the psychiatric conditions are exhibited. Even though every effort is exerted to extend emotional support to the individual, there still persist various unavoidable

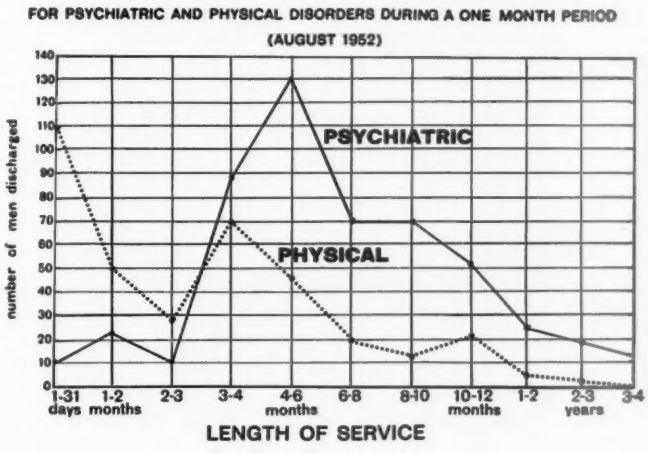

FIG. 2.

stressful situations, which reverberate in organ responses to bring forth other physical conditions. This is reflected on the graph by the second elevation of the physical line.

In recent years there has been more effective utilization of manpower, especially with respect to psychiatrically marginal individuals. Psychiatric rejections for the military service in World War II, 1942 through 1945, accounted for approximately 24 per cent of all medical rejections, as opposed to 12.8 per cent during the Korean incident, 1950 through 1953. Of the total Navy and Marine Corps medical discharges for the periods, the psychiatric percentages were 34 and 38, respectively. This means that during the process of absorbing 11.2 per cent more psychiatrically-marginal individuals during the Korean incident, the discharge rate was increased by only 4 per cent. The remaining 7.2 per cent completed a normal period of naval service.

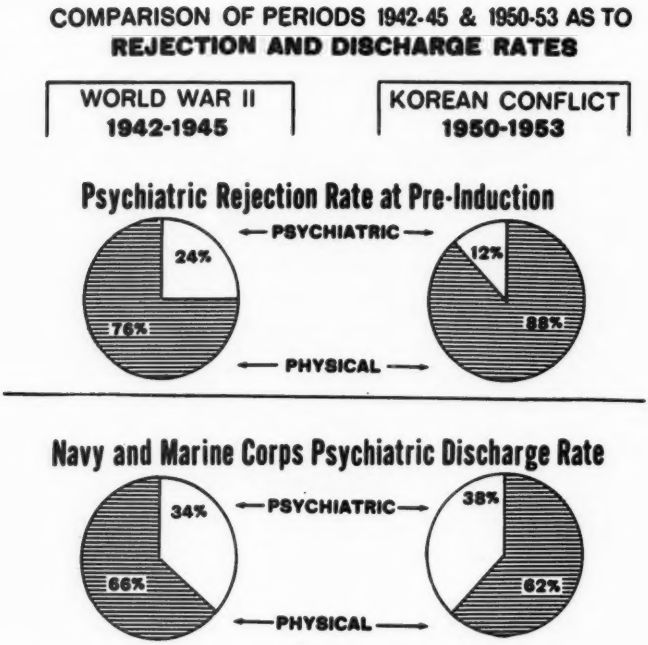
COMPARISON OF PERIODS 1942-45 & 1950-53 AS TO
REJECTION AND DISCHARGE RATES
WORLD WAR II
1942-1945
KOREAN CONFLICT
1950-1953
Psychiatric Rejection Rate at Pre-Induction
PSYCHIATRIC
24%
76%
PHYSICAL
12%
88%
Navy and Marine Corps Psychiatric Discharge Rate
PSYCHIATRIC
34%
66%
PHYSICAL
38%
62%

FIG. 3.

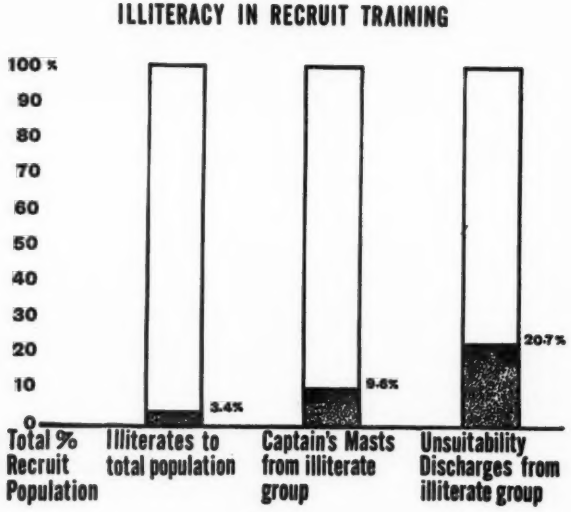
ILLITERACY IN RECRUIT TRAINING
100 %
90
80
70
60
50
40
30
20
10
0
3.4%
9.6%
20.7%
Total % Recruit Population
Illiterates to total population
Captain's Masts from illiterate group
Unsuitability Discharges from illiterate group

FIG. 4.

Illiteracy, a term which continues ill-defined, constitutes a distinct problem. In World War II, 3.4 per cent of all recruits were considered illiterates, that is, they had not achieved the performance level of a fourth-grade education. This group, however, averaged an exposure to education through the fourth grade. From this illiterate group came 9.1 per cent of all Captain's Masts and 20.7 per cent of all unsuitability discharges. Today it is apparent that the lack of an opportunity to obtain an education is less prominent in illiteracy, while such factors as emotional disturbances, lack of motivation and psychiatric illness are more prominent.

A comparison study was made of a group of marginal individuals with a control group of normals, both successfully completing a period of three years of naval service.[7] These cases were originally studied in 1943 by

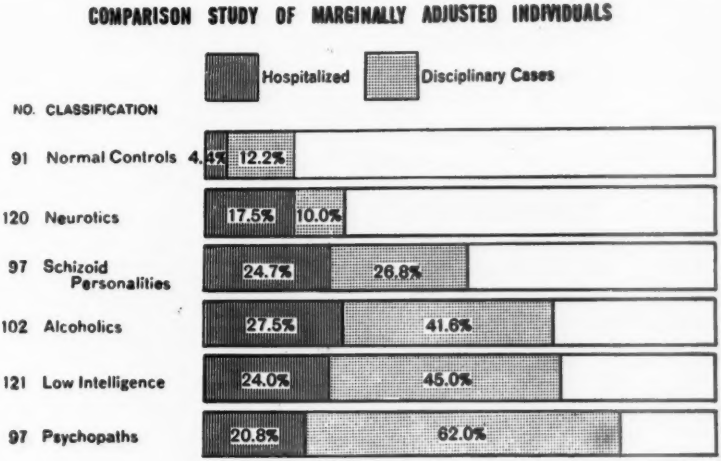

FIG. 5.

the psychiatric unit of the same training center, and evaluation was concurred in each case by at least two psychiatrists. This survey reveals that, despite the successful completion of the three-year period of service, the marginal group had a much higher incidence of hospitalization and disciplinary difficulties.

Another study recently conducted clearly indicates the efficiency of Navy selection procedures as now conducted and the cost of utilizing substandard personnel. In the calendar year 1948, about 1.6 per cent of all incoming recruits were recommended to the Aptitude Boards by the psychiatric units for discharge from the Service. The Boards, which are administrative and nonmedical, did not concur in about 10 per cent (or 217 referred recruits), and returned them to duty. A detailed follow-up study of each of the 217 recruits was carried out over the entire three-year period that followed.[8]

One half of these individuals completed the three-year period but not one made an advancement to a petty officer rate. The other one half was discharged with an average of nine months of service; 34 received medical surveys for psychiatric conditions, averaging 78 days each on the sick list and accumulating multiple disciplinary offenses; the remaining 75 of this one half received administrative discharges for one reason or another.

Even though such individuals are meeting the group adjustmental standards, they are doing so at a greater cost to the group's medical and disciplinary facilities, as well as creating a greater friction upon the group's social organization. In dollars and cents the cost is considerable.[5] If the 109 of the 217 recruits in this study who were prematurely discharged had been separated at the time of the medical recommendation, the cost would have

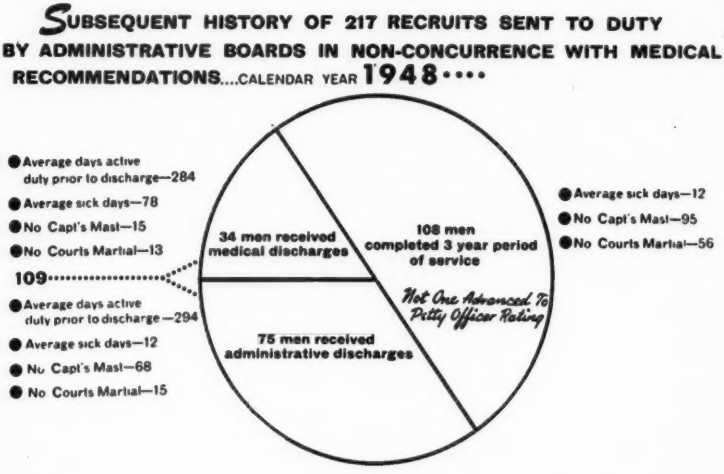

FIG. 6.

been $6,300. After an average of nine months' service, however, the actual cost of discharging this group was $35,600, or $9,000 for the 75 administratively discharged and $26,600 for the 34 medically discharged. Repeated studies of this type conclusively show that there are incidental or "hidden" costs incurred in the utilization of the marginal group. They exert a greater drain on medical, disciplinary and educational facilities, even though they successfully complete their period of enlistment. When this group is utilized it is necessary to provide for the additional demands they make. The question then arises as to whether the service rendered by the members of the marginal group who completed a so-called normal period of service warrant the cost involved in the high percentage of failures therein? The answer lies in the exigencies of the situation at the time, and as it affects manpower shortage.

While it is true that these United States have enormous natural resources and economic reserves, it is a commonly held belief that they are inexhaustible. Manpower, however, is one resource that is always in scarce supply in time of war. In the utilization of marginal manpower more calculated risks are deliberately taken, resulting in increased costs and higher taxes. Thus, in times of manpower shortage, when the use of marginal personnel is inevitable, every effort should be exerted to employ this group to the greatest advantage, with the least expenditure and disruption. This can be accomplished only by long-range planning based on the assumption that in all subsequent national emergencies the marginal, substandard and handicapped individuals will be utilized.

There is one cost that we must always guard against, and one that our country cannot afford—the cost to us if we lost our next war. In our constant struggle to accomplish broad social aims, let us not forget that you cannot beat off a lion with a cream puff, and that it is not wise to send a boy to do a man's job. It is essential that the first line of defense of our freedoms be manned with personnel who can effectively produce. While other goals may be established, the first objective of this country is to win its wars, and it is our responsibility to provide the quality of manpower that will ensure attaining this objective.

BIBLIOGRAPHY

1. Ling, T. M., Zausmer, D. M., and Hope, M.: Occupational rehabilitation of psychiatric cases; follow-up study of 115 cases, Am. J. Psychiat. **109**: 172–176 (Sept.) 1952.
2. Frazer, R., Bunbury, E., Daniell, B., Barling, M. E., Waldron, F. E., Kemp, P. M., and Lee, I.: Incidence of neurosis among factory workers, Industrial Health Research Board, Report No. 90, 1947, His Majesty's Stationery Office, London.
3. Egan, J. R., Jackson, L., and Eanes, R. H.: Study of neuropsychiatric rejectees, J. A. M. A. **145**: 466–469 (Feb. 17) 1951.
4. Brill, N. Q., and Beebe, G. W.: Some applications of follow-up study to psychiatric standards for mobilization, Am. J. Psychiat. **109**: 401–410 (Dec.) 1952.
5. Research studies conducted by the Neuropsychiatry Branch of the Professional Division, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., 1949–1954.
6. Hunt, W. A., Wittson, C. L., and Burton, W. B.: Validation study of naval neuropsychiatric screening, J. Consulting Psychology **19**: 35–39 (Feb.) 1950.
7. Hunt, W. A., Wittson, C. L., and Hunt, E. B.: Military performance of group of marginal neuropsychiatric cases, Am. J. Psychiat. **109**: 168–171 (Sept.) 1952.

FIBROPLASTIC ENDOCARDITIS WITH EOSINOPHILIA (LÖFFLER'S ENDOCARDITIS PARIETALIS FIBROPLASTICA): CASE REPORT AND REVIEW OF LITERATURE *

By F. G. Hoffman, Lt. Colonel, USAF (M.C.), *Waterloo, N. Y.*, David Rosenbaum, M.D., and P. D. Genovese, M.D., *Indianapolis, Indiana*

In 1936 Löffler published a report of two patients with a hitherto unclassified type of endocarditis.[1, 9] This entity, subsequently referred to as fibroplastic endocarditis or Löffler's endocarditis parietalis fibroplastica, is characterized by an afebrile course, progressive, refractory congestive failure and a striking eosinophilia. The cases reported by Löffler, in addition, exhibited signs of mitral valvulitis, though these were inadequate to account for the clinical picture.

Until 1948 only six cases had been reported, all in the Swiss and German literature. Lennox [2] called attention to this entity and published a report of a possible early stage of Löffler's endocarditis.

The following case report is based on clinical and pathologic observations of a patient who exhibited the features of this entity.

Case Report

History: The patient, a 23 year old white male postal clerk, was first admitted to the surgical service of the hospital in August, 1949, with the complaints of right lower quadrant abdominal pain, nausea and vomiting.

The past medical history was negative for rheumatic fever or its equivalents. The patient had been accepted for military service in 1947, and physical examination and chest x-ray were then recorded as normal (figure 1). He served in the Armed Forces for seven months within the continental limits of the United States and never left the country.

Physical Examination: Physical examination revealed a well developed, well nourished male who appeared to be in moderate pain. Examination of the heart was negative. Blood pressure was 128/76 mm. of Hg. There was moderate localized tenderness in the right lower quadrant of the abdomen.

Laboratory Examinations: Urinalysis was negative. White blood count was 21,000 per cubic millimeter, with 7% eosinophils. Coagulation time was six minutes; prothrombin time was 70% of normal, and the blood platelet count was 280,000. Several stool specimens were negative for ova, parasites and blood.

The patient had an abdominal exploration, and the surgeon described moderate mesenteric lymphadenitis. The appendix was resected, and microscopic studies of

* Received for publication April 26, 1954.
From the Veterans Administration Hospital, Indianapolis, Indiana.
Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

the appendix revealed an unusual amount of old and recent hemorrhage within the wall. The patient recovered uneventfully from surgery and was discharged on September 27, 1949.

He was re-admitted on June 6, 1950, complaining of increasing dyspnea, generalized cramping, abdominal pain, and diarrhea of one month's duration. Examination at that time revealed an acutely ill male who was moderately cyanotic, dyspneic and orthopneic. There were fine crepitant râles at both lung bases. The point of

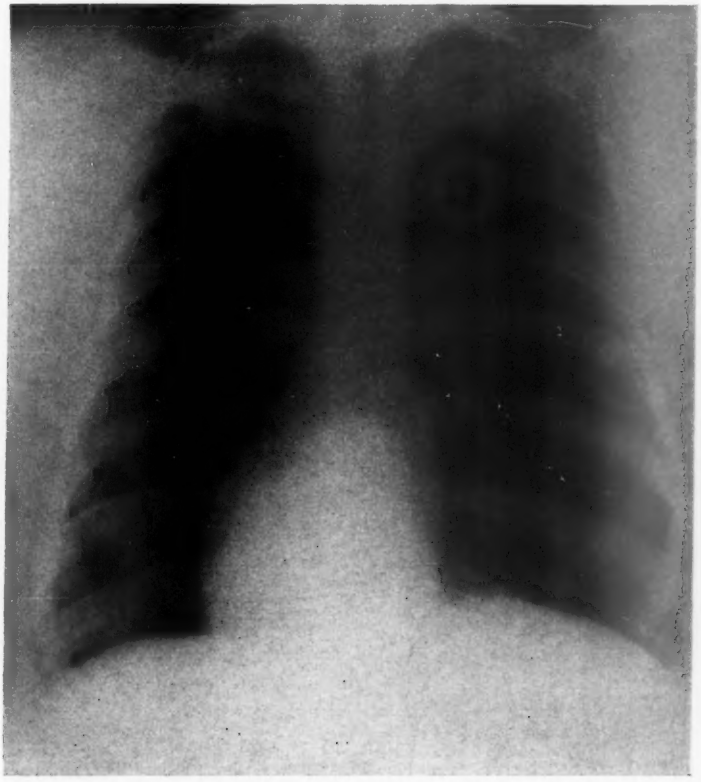

FIG. 1. X-ray of the chest (1947), revealing no abnormality of the heart or lung.

maximal impulse was in the fifth interspace in the left anterior axillary line. There was a systolic thrill and murmur and a low pitched diastolic rumble over the apical area. The liver was palpable 7 cm. below the costal margin, and the spleen was also easily palpable 5 cm. below the costal margin.

Laboratory studies showed a white blood count of 12,000 per cubic millimeter, with 65% eosinophils, 25% lymphocytes and 10% neutrophils. Bone marrow examination revealed a granulocytic hyperplasia of the eosinophilic elements. A gastrocnemius biopsy was negative. X-ray examination of the chest revealed moderate cardiac enlargement, with fluid in the right base (figure 2). Cardiac fluoroscopy was reported

as negative except for slight enlargement of the left auricular segment. Electrocardiogram revealed prominent P waves in the standard leads, and large R waves in V_1 and aVR in the precordial leads consistent with a right ventricular hypertrophy pattern (figure 3). There were no other significant laboratory findings. The patient improved on routine cardiac management and was discharged on July 5.

From March, 1951, to March, 1952, the patient was re-admitted to the hospital eight times for repeated bouts of congestive failure. Each attack became increasingly resistant to therapy and, during the last six months of the illness, was characterized by marked peripheral edema and dyspnea. Physical examinations were essentially

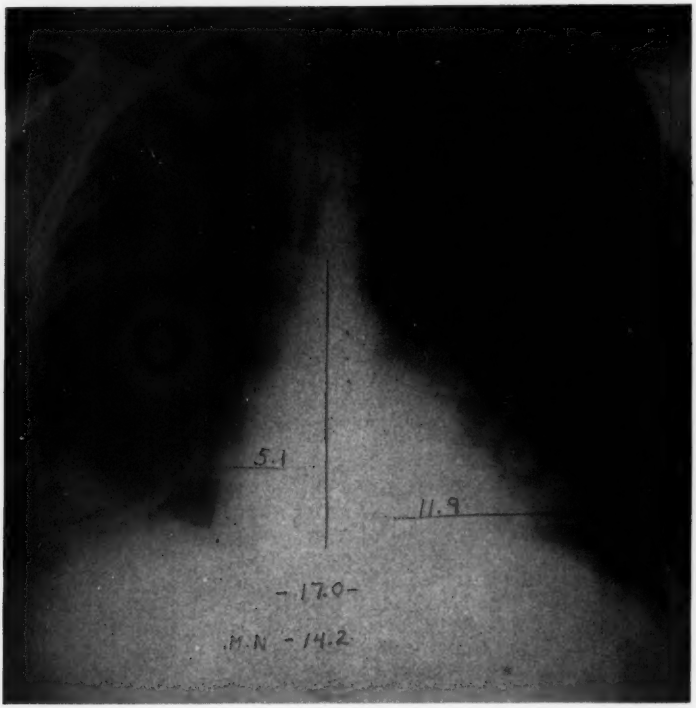

FIG. 2. X-ray of the chest dated June 24, 1950, revealing cardiac enlargement with fluid in the right base.

the same as on previous admissions. There was no change in the murmurs, and hepatomegaly and splenomegaly were persistent. During these admissions repeated white blood counts revealed a total white count which varied from 15,000 to 21,000 per cubic millimeter, accompanied by an eosinophilia which varied from 50% to 70% of the total white count. Bone marrow studies were described as being the same as in 1950. A liver biopsy in 1951 was interpreted as normal. X-ray of the chest in October, 1951, showed straightening of the left border of the cardiac wall, with an increase in the size of the heart as compared to June 24, 1950 (figure 4).

On his last admission to the hospital the patient appeared chronically ill and was dyspneic and cyanotic. Blood pressure was 128/76 mm. of Hg; pulse was 100.

There was marked distention of the neck veins and the sublingual veins. There was dullness at the base of the right lung. The previously described murmurs were essentially the same. P_2 was accentuated over A_2. The liver was palpable three fingerbreadths below the costal margin. There was no apparent change in the size of the spleen. There was marked pitting edema of both lower extremities up to the level of the knees.

Laboratory studies revealed a white blood count which varied from 14,500 to 17,500 per cubic millimeter, with eosinophils from 45% to 70%. There was 9% retention of bromsulfalein dye in 45 minutes. Prothrombin time was 65% of normal. Other liver function studies, blood cultures and stool examinations were all reported as negative. X-rays of the chest revealed no significant increase in the size of the heart, and there were signs of fluid in the right base.

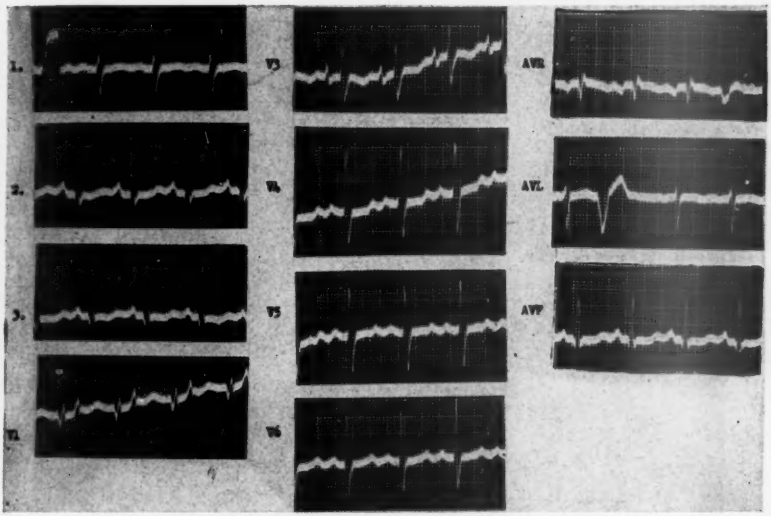

FIG. 3. Electrocardiogram revealing high voltage P waves and late R waves in V_1 and aVR.

The patient was treated with oxygen, Demerol, digitalis, ammonium chloride and mercurial diuretics. His response to treatment was very poor. The dyspnea seemed to improve but the leg edema persisted. During the terminal part of his illness the patient developed gradually increasing azotemia with low chlorides and low sodium. His course was progressively downward, and he died on July 5, 1952, approximately three years after the onset of the illness.

Autopsy: Autopsy was performed nine hours after death. There was a considerable amount of edema of the lower extremities and genitalia. The peritoneal cavity contained 1,000 c.c. of clear, straw-colored fluid; the right pleural cavity contained 2,000 c.c., the left, 1,000 c.c. of similar fluid. A moderate amount of pulmonary edema was noted, and there was evidence of chronic passive congestion in the lungs. The pericardium was normal, but the sac contained 125 c.c. of clear, straw-colored fluid. The heart weighed 300 gm. The right side was noted to be dilated. This dilatation was particularly marked in the outflow tract of the right ventricle and in the right atrium. A few minute foci of grayish brown fibrosis were present beneath

the endocardium of the right atrium. An enormous locus of fibrosis involving the anterolateral wall of the right ventricle downward from the tricuspid valve to the apex was present, and this extended to the anterior portion of the interventricular septum (figure 5). The fibrosis was very pale and dense and of almost cartilaginous consistency. It involved the endocardium and extended for some little distance into the inner portion of the myocardium. No fibrosis was noted in the rest of the myocardium of the right ventricle. The mitral valve orifice was somewhat narrowed,

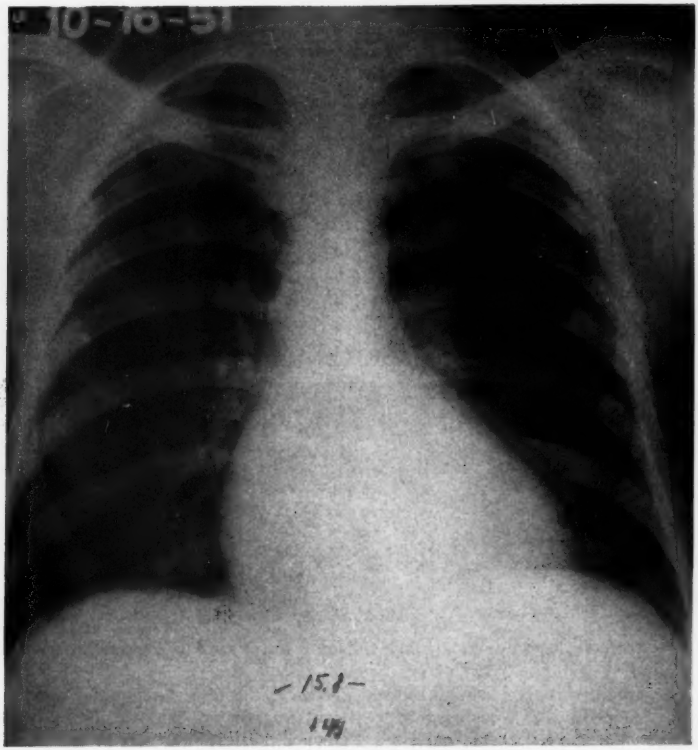

FIG. 4. X-ray of the chest revealing straightening of the left border of the heart, with increasing size of the heart since 1950.

and just above the valve, on its superior aspect and extending on to the auricular wall, there was a large amount of brownish, fairly firm granular material which resembled an old thrombus. This was firmly adherent to the upper aspect of the mitral valve and to the adjacent auricular endocardium (figure 6). The left ventricular wall was thinner than usual and showed some patchy fibrosis just beneath the endocardium, particularly on the posterior wall. A small amount of fibrosis was also noted in the outflow tract, just below the commissure between the left and right coronary cusps (figure 7). The tricuspid valve orifice measured 12.5 cm. in circumference and showed considerable fibrosis, involving the valve, the chordae

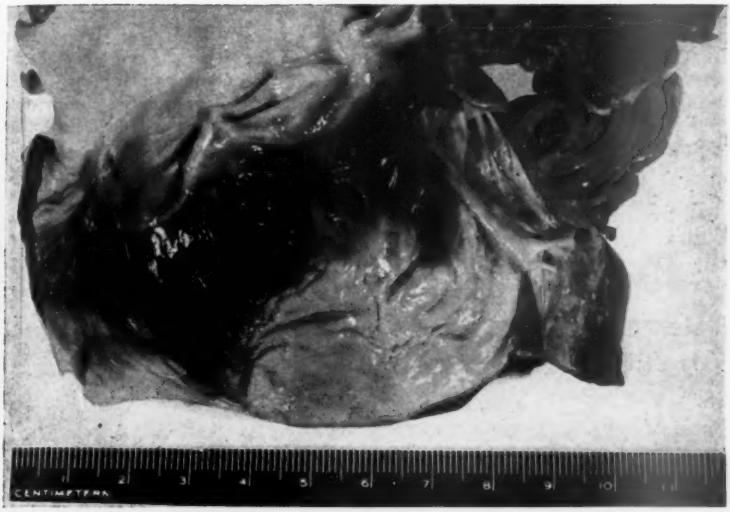

FIG. 5. Anterior of the right ventricle showing extensive fibrosis of the endocardium and subendocardial myocardium.

tendineae and the papillary muscles. This fibrosis was continuous with that in the wall of the right ventricle. The attachment of the tricuspid valve was abnormally low, so that at its posterior extremity it was placed only 2.5 cm. above the apex of the ventricle. The mitral valve measured 7 cm. in circumference and was con-

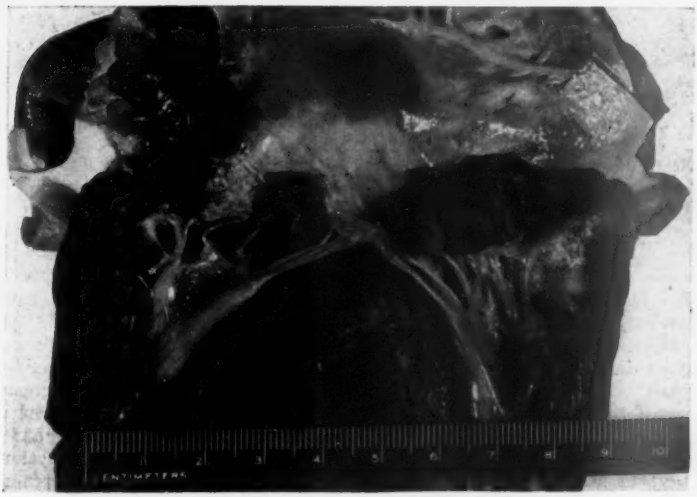

FIG. 6. Chambers of the left side of the heart and mitral valve, showing large mitral and left auricular vegetations.

siderably thickened. The cusps were very opaque and gray, and there were thickening, shortening and adhesions of the chordae tendineae. In some places the papillary muscles reached almost to the edge of the valve, and they also showed some fibrosis (figure 6). The aortic valve exhibited a series of vegetations which were present on all of the cusps. These were verruca-like and firm. They occurred chiefly at or near the line of closure, although on the right coronary cusp they extended downward beyond the line of closure. These vegetations were a pale yellowish gray in color, and could be broken or removed very easily. The aortic valve cusps showed some rolling down of the free edges, with slight shortening but no significant adhesions of the commissures. No valvular calcification was noted. The coronary arteries exhibited no abnormalities. The aorta and large arteries and veins showed no gross changes. The spleen weighed 600 gm. and showed evidence of numerous ischemic infarcts and chronic passive congestion. The liver weighed 2,200 gm. Its surface

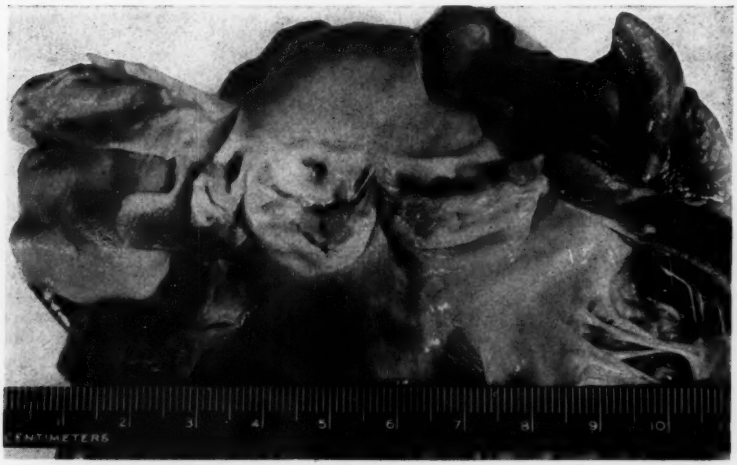

FIG. 7. Aortic valve showing slight fibrosis and verruca vegetations on all leaflets.

was finely and coarsely nodular in appearance. On cut section the lobular architecture was easily discerned. There appeared to be an increased amount of fibrosis in the liver. The central portions of the liver exhibited dark mottling consistent with chronic congestion.

Sections of the right atrium revealed subendocardial fibrosis. The myocardial fibers were slightly hypertrophied. The epicardium was not remarkable. There was no evidence of inflammatory changes of significance. Other sections through the heart revealed some areas of focal fibrosis in the myocardium and some hypertrophy of muscle fibers. There were occasional infiltrative inflammatory cells within the myocardium. These were chiefly lymphocytes with a few neutrophils. No eosinophils were recognized. The small vessels were not remarkable. Sections of the heart through the right ventricle showed a very thick mass of hyalinized connective tissue beneath the endocardium extending for a great distance into the myocardium (figure 8). No myocardial fibers were recognized within this hyalinized connective tissue. The subjacent myocardium was not remarkable in appearance, although occasional minute foci of fibrosis were seen. The epicardium in this area was not unusual. Sections through the mitral valve showed the enormous mass of

thrombotic material which was described grossly (figure 9). This consisted of amorphous debris in which there were clumps of red blood cells, some of which appeared to be in recanalized channels. The underlying auricular musculature showed a considerable amount of diffuse interstitial fibrosis, and no specific inflammatory changes were noted except in the region of the thrombus, where there were some lymphocytes. Section through the aortic valve revealed an amorphous fibrinous deposit near the end of the valve which corresponded to the vegetations noted in the

FIG. 8. Section through right ventricle showing extensive endocardial fibrosis.

gross examination. The myocardial fibers in the left ventricle were hypertrophied, and there was a considerable degree of fibrosis in the valve ring area. No inflammatory changes were noted.

Examination of the aorta showed no significant abnormality, and a section through a medium sized artery showed no evidence of atherosclerosis or other change. No evidence of recent or old inflammatory changes was noted, and no eosinophils were seen.

Sections through the lung revealed a considerable degree of atelectasis and some interstitial fibrosis, particularly in those sections through the lower lobes. Occasional

foci of lymphocytes were noted. Many of the alveoli contained large numbers of pigment-laden phagocytes, indicative of chronic passive congestion. The larger vessels, especially the veins, were considerably distended. Occasional small thrombi were noted in the vessels.

Microscopic examination of the spleen revealed numerous small foci of fibrosis with hyalinization. In addition, there was evidence of extensive infarction. Some of these infarcts were apparently hemorrhagic, since they contained a considerable

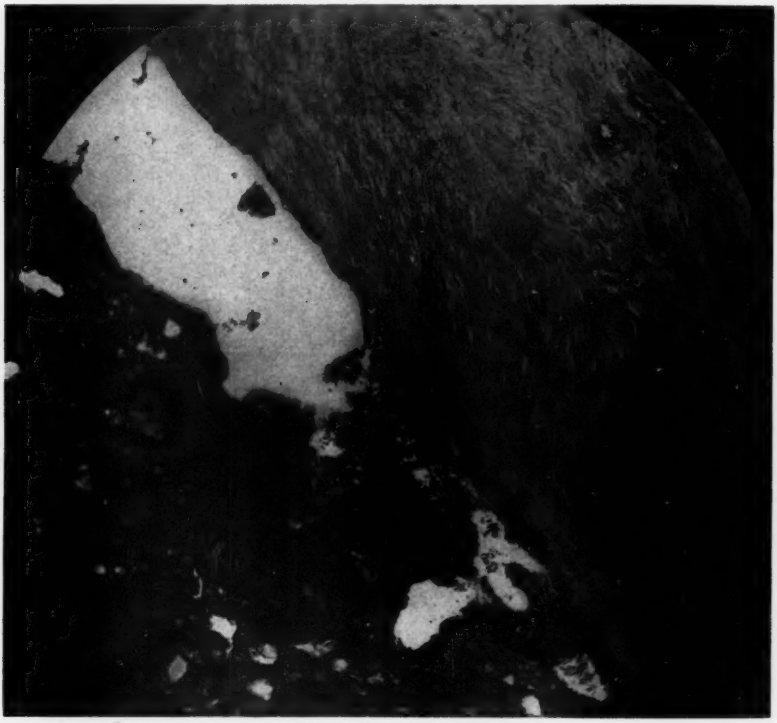

FIG. 9. Section through mitral valve showing large adherent and partially vascularized thrombus.

amount of golden brown pigment. The sinusoidal endothelium within the pulp was prominent, indicative of chronic passive congestion.

The liver showed profound disturbance of the architecture, due to the presence of streaks of collagenous connective tissue which subdivided the hepatic parenchyma into pseudo-lobules. Some of these nodules exhibited marked dilatation of the sinusoidal spaces and others were relatively ischemic. Some of the connective tissue contained somewhat proliferated bile ducts and a few lymphocytes. The nodules of hepatic parenchyma varied considerably in size and shape. The appearance was that of a cirrhosis which may have been based on severe chronic congestion over a long period of time. Sections through the lymph node, some of which were from the tracheo-bronchial area, others from the peripancreatic region, showed similar archi-

tectural changes. There was a considerable number of infiltrative eosinophils, together with some phagocytes, in which there were abundant amounts of brown blood pigment. The eosinophilia was rather striking. Also present in the peripancreatic fat near the lymph nodes were a considerable number of lymphocytes and some eosinophils.

Discussion

During this patient's lifetime there was considerable division of opinion as to the nature of the cardiac lesion. There was no history of rheumatic fever or its equivalents. In spite of the persistent cardiac apical murmurs, the heart size in the presence of severe congestive failure never enlarged to proportions that one might expect with rheumatic mitral stenosis and insufficiency. The collagen group of diseases was considered but, except for the eosinophilia, there was little to support the diagnosis of any one of these entities. Lymphoma, atrial myxoma and primary systemic amyloidosis were all considered. However, this group of diseases would not account for the marked eosinophilia and splenomegaly, which seemed to be out of proportion to the congestive failure. The final medical opinion prior to the patient's death was that we were probably dealing with two entities instead of one. It was not until almost a year after the patient's death that one of us (P. D. G.) finally realized the true nature of the patient's illness, namely, fibroplastic endocarditis with eosinophilia. This case is apparently the first reported in the American literature. Search of the medical literature revealed that the first cases were reported by Löffler [1] in 1936 in the Swiss literature. Our case closely parallels clinically and pathologically the salient features described by Löffler. The patient's course was an afebrile one, with progressive, chronic congestive failure. Cardiomegaly was not the prominent feature one might have expected in comparison with the degree of failure. Apical systolic and diastolic murmurs persisted to the end and were confirmed by all examiners. The eosinophilia varied from 30% to 70% of the peripheral white blood count and remained a constant finding. Löffler's pathologic findings were a peculiar fibrotic parietal endocarditis grossly involving both ventricles and septum which was most marked in the right ventricle and which contained mural thrombi. Both atria were markedly dilated without gross or microscopic lesions. The mitral ring was dilated, but the valve was free of inflammatory lesions. There were changes consistent with severe chronic passive congestion of the viscera, and the bone marrow exhibited a marked eosinophilia.

The acquired types of endocardial sclerosis, according to Gould,[3] result from primary myocardial lesions, hypertension, congenital anomalies of the coronary arteries and inflammatory conditions. Similar lesions have been described in idiopathic cardiac hypertrophy,[5] beriberi heart disease [6] and other entities.[4, 21] In almost all of these the endocardial sclerosis was most marked in the left ventricle.

In the recent pediatric literature considerable attention has been focused on the subject of the endocardial fibro-elastosis. These are believed to be developmental anomalies rather than acquired inflammatory lesions.[2, 8] Many reviews of the subject are available,[10, 11, 12] and it is noted that this type of lesion is similar pathologically to the other types, and that the difference is one of degree. Also, all the reported cases have shown that the process is confined to the endocardium of the left ventricle.

Lennox [2] in 1948 reported a case of a 53 year old woman who died in status asthmaticus. The total eosinophil count varied from 500 to 700 per cubic millimeter during the last week of her illness. At autopsy the heart weighed 340 gm., and there was moderate right-sided dilatation. The right ventricular wall measured 4 mm., the left 1 to 2 cm. All the valves and the coronary arteries were normal. Microscopically, the endocardium of the left ventricle showed widespread changes, with swelling and irregularity of the endothelial cells. The more advanced lesions were found beneath the endocardium. It was the opinion of Lennox that this case possibly represented an early stage of fibroplastic endocarditis, and that only the complicating mural thrombosis was needed to duplicate the final results seen in more advanced stages. Lennox has summarized the salient features of six previously reported cases. Two more have been reported by Gray,[16] and although both of his patients resided in Africa at the onset of their illness, it was his opinion that the eosinophilia could not be attributed to parasitic infection. He also stressed the greater frequency of this disease in the Africans.[17] In the eight cases previously reported there were six males and two females, ranging in age from 25 to 49 years. The duration of illness extended from two weeks to two and one-half years. Eosinophil count in the peripheral blood ranged from 1,170 to 39,500 per cubic millimeter. In all of these the course was one of progressive cardiac failure, with insignificant cardiomegaly or cardiac murmurs. The autopsy findings showed massive fibrosis of the right ventricle in five cases, and in four of these there was an organizing thrombus on the surface. In two there was massive fibrosis of the left ventricle, with an organizing endocardial thrombus in both. In one there was involvement of the endocardium of the right atrium; in another there was a thickened mitral valve, and in another there was thickening of both the mitral and tricuspid valves, with wartlike vegetations.[19, 20, 23, 25]

The etiology and pathogenesis of this condition are still unknown. Löffler originally suggested an allergic manifestation, in view of the marked eosinophilia. In one case [22] *Streptococcus viridans* was cultured from the blood and other organs and suggested the possibility of an inflammatory origin. Harkavy [7] also proposed that hypersensitivity to some fundamental infection may be causative in the cases reported by Löffler. Prior and Wyatt [13] felt it unlikely that an infectious process would selectively involve the endocardial tissue of a specified region of the heart. In our case no eosinophils were found on microscopic examination of the heart muscle. This entity has also been related to endarteritis obliterans, but very few authors support this concept.[20]

Prior [24] recently reported two cases of anomaly of the mitral valve with fibro-elastosis. In one of these there was no cardiac embarrassment until the age of 26 years. It is possible that in our patient some superimposed illness precipitated the final episode which eventually culminated in myocardial failure and death. There was no evidence of any heart disease prior to 1949, and the onset of the patient's illness seems to date to August, 1949, following what was thought to be an acute appendicitis. The cause of death appeared to be progressive right ventricular failure, and the mitral lesion seemed to contribute to only a minor degree. Using the suggestion of Weinberg and Himmelfarb,[14] we propose that ventricular anoxia developed because of the interference with proper emptying of the arterioluminal vessels due to marked fibrosis of the ventricular

wall. As a result of the extensive endocardial fibrosis, which involved the tricuspid valve, the chordae tendineae and the papillary muscles, proper functions of these structures were impeded, with ensuing right ventricular failure. Prior and Wyatt [13] offered an interesting analogy by comparing the thickened rigid endocardium to constructive pericarditis, in which the endocardial alterations tend to "limit both the diastolic filling and systolic expulsion of the involved ventricle."

Summary

1. A case is presented of fibroplastic endocarditis with eosinophilia in a 23 year old white male which simulated in detail the eight previously reported cases. This is believed to be the ninth case reported in the medical literature and the first in the United States.

2. The clinical characteristics of this entity are:

A. An afebrile course.

B. Progressive refractory chronic congestive failure.

C. Cardiac findings disproportionate to the degree of heart decompensation.

D. Persistent and striking eosinophilia in the bone marrow and lymphoid tissues.

3. The etiology and pathogenesis of this entity are unknown. The possible etiologic factors have been briefly reviewed.

4. The dynamics involved in the production of cardiac failure were briefly discussed.

BIBLIOGRAPHY

1. Löffler, W.: Endocarditis parietalis fibroplastica mit Blut eosinophile, Schweiz. med. Wchnschr. **66**: 817, 1936.
2. Lennox, B.: Acute parietal endocarditis in a case of status asthmaticus: a possible early stage of Löffler's endocarditis parietalis fibroplastica with eosinophilia, J. Path. and Bact. **60**: 621, 1948.
3. Gould, S. E.: Pathology of the heart, 1953, Charles Thomas, Springfield, Ill.
4. Smith, J. J., and Furth, J.: Fibrosis of myocardium with mural thrombosis: notes on its relation to isolated (Fiedler's) myocarditis and to beri-beri, Arch. Int. Med. **71**: 602, 1943.
5. Case Records, Mass. General Hospital, Case 39441, New England J. Med. **249**: 734 (Oct.) 1953.
6. Benchimal, A. B., and Schlesinger, P.: Beri-beri heart disease, Am. Heart J. **46**: 245 (Aug.) 1953.
7. Harkavy, J.: Vascular allergy: pathogenesis of bronchial asthma with recurrent pulmonary infiltration and eosinophilic polyserositis, Arch. Int. Med. **47**: 209, 1941.
8. Golper, M. N.: Endocardial fibro-elastosis, Radiology **61**: 865, 1953.
9. Friedberg, C. K.: Diseases of the heart, 1950, W. B. Saunders Co., Philadelphia.
10. Adams, F. N., and Katz, B.: Endocardial fibro-elastosis, J. Pediat. **41**: 141, 1952.
11. Collier, F. C., and Rosahn, P. D.: Endocardial fibro-elastosis, Pediatrics **7**: 175, 1951.
12. Cosgrove, G. E., and Kaump, D. H.: Endocardial sclerosis in infants, Am. J. Clin. Path. **16**: 322, 1946.
13. Prior, J. T., and Wyatt, T. C.: Endocardial fibro-elastosis: a study of eight cases, Am. J. Path. **26**: 969 (Nov.) 1950.
14. Weinberg, T., and Himmelfarb, A. J.: Endocardial fibro-elastosis (so-called fetal endocarditis), Bull. Johns Hopkins Hosp. **72**: 299, 1943.

15. Reinhart, W.: Die isolierte diffuse interstitielle eosinophile Myokarditis, Cardiologia 11: 219, 1947.
16. Gray, I.: Endocardial fibrosis, Brit. Heart J. 13: 387 (July) 1951.
17. Davies, J. N. P.: Endocardial fibrosis in Africans, East African M. J. 25: 10, 1948.
18. Löffler, W.: Pathogenetic significance of the so-called endocarditis parietalis fibroplastica, Bull. schweiz. Akad. d. med. Wissensch. 2: 287, 1946–7.
19. Roulet, F.: Beitrag zur Kenntnis der Endocarditis parietalis fibroplastica mit Bluteosinophile (Löffler), Schweiz. med. Wchnschr. 74: 427, 1944.
20. Mumme, C.: Zur Klinik und Pathologie der Endokarditis und Aortitis fibroplastica sowie Thromboendarteritis obliterans mit hochgradiger Eosinophilie im Blut, Knochenmark und in den Organen, Ztschr. f. klin. Med. 138: 22, 1940.
21. Medical Grand Rounds Case 187: Familial idiopathic hypertrophy of the heart: ACTH treatment, Am. Pract. and Digest Treat. 2: 890, 1951.
22. Deus, P.: Ueber Sepsis lenta, Cor.-Bl. f. Schweiz. Aerzte 46: 1473 (Oct.) 1916.
23. Egger, P.: Endocarditis obliterans. Ihre Beziehungen zur Endocarditis parietalis fibroplastica mit Bluteosinophile und zum Morbis Buerger, Schweiz. Ztschr. f. Path. Bakt. 7: 237, 1944.
24. Prior, J. T.: Congenital anomalies of the mitral valve, Am. Heart J. 46: 649 (Nov.) 1953.
25. Buchler, H.: Eosinophile, Mikrobielle Endoallergie. Ein einheitlicher klinisch-pathogenetischer Formenlsresis, Ztschr. f. klin. Med. 140: 56–73, 1941.

PAROXYSMAL VENTRICULAR TACHYCARDIA IN AN APPARENTLY NORMAL HEART *

By Alfred Ring, M.D., and Julius Blankfein, M.D., *New York, N. Y.*

Paroxysmal ventricular tachycardia in a patient without demonstrable organic heart disease is comparatively rare. Armbrust and Levine [1] in a review of 107 cases reported no organic heart disease in 13. This series included all cases seen at the Peter Bent Brigham Hospital and in the private practice of the latter author from 1915 to 1948. At the Massachusetts General Hospital, Cooke and White [2] found only 24 cases of paroxysmal ventricular tachycardia among 51,000 records of 25,000 patients in the cardiographic laboratory over a period of 25 years, from 1914 to 1939. Of these 24 cases, four had apparently normal hearts. On the other hand, at a third Boston institution, the Boston City Hospital, Williams and Ellis [3] noted only one patient with no organic heart disease in an analysis of 36 cases of paroxysmal ventricular tachycardia. However, most other records indicate an incidence of 10% or more of apparently normal hearts with this arrhythmia. Thus, Herrmann and Hejtmancik [4] found two cases in 20. In a review of the literature in 1934, Lundy and McLellan [5] noted 13 cases with no demonstrable heart disease out of 96 cases. In a 1930 article, Strauss [6] found no clinical or laboratory evidence of heart disease in 11 cases out of 64 in the literature.

The case of paroxysmal ventricular tachycardia herewith reported is considered of special interest not only because of the absence of any apparent organic

* Received for publication April 27, 1954.
From the Medical Service of Queens General Hospital, Jamaica, N. Y.

heart disease but also because of the probable relationship of the attacks to emotional strains.

Case Report

A 34 year old married German, an orthopedic appliance worker, was first admitted to Queens General Hospital on July 15, 1952, because of palpitation of 10 days' duration, and associated weakness, dyspnea and swelling of the ankles. He had served in the German army for five years during World War II, and was taken prisoner by the United States Forces. In January, 1945, although his health had previously been good, he was quite run down and his weight was down to 95 pounds. While in a prisoner-of-war camp in Germany a few weeks later he noted the first attack of rapid beating of his heart. At that time he was conscious of the attack by a pounding in his chest to such a degree that he himself noted the wide excursion of a handkerchief applied to the precordial region. This first attack lasted about 15

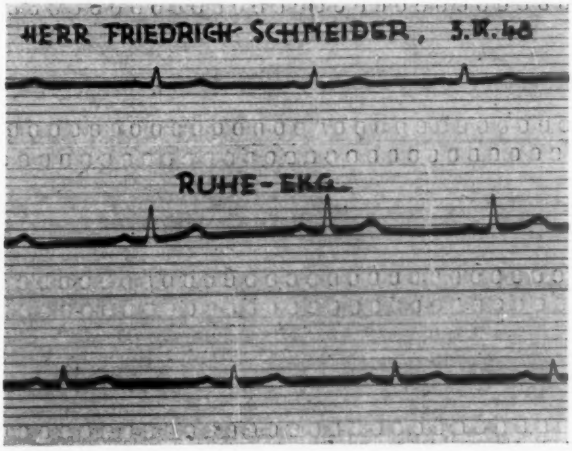

Fig. 1. Electrocardiogram taken while at Bad Nauheim, Germany, on September 3, 1948: entirely normal.

minutes. Six months later, after being released as a prisoner-of-war and while in an open box car en route to his home, he had a second attack lasting about the same length of time. A local doctor took an electrocardiogram and made a diagnosis of ventricular tachycardia. In 1948, as an out-patient in Bad Nauheim, he had two attacks which were studied (figures 1 and 2). All of these early attacks began abruptly and terminated in a similar manner. Their duration varied from 15 minutes to several hours. Between attacks the patient felt fairly well and had no dyspnea on exertion, angina or ankle edema. Fatigue, exertion and emotional strain seemed to precipitate the episodes of palpitation. No relief was afforded by eyeball pressure, carotid pressure or vomiting.

His past medical history was essentially negative except for a right eye injury in childhood which caused loss of most of the vision in this eye, and an attack of trench foot lasting four months while he was at the Russian front in 1941. There was no history of rheumatic fever, rheumatism or any cardiac disturbance prior to 1945.

Up to 1952 the patient smoked one to two packs of cigarettes per day, had a few cups of coffee daily, and an occasional drink. However, since that time he has given up coffee and cigarettes completely, and has just one bottle of beer each evening.

In December, 1951, he came to the United States with his wife and two children. For two years prior to this, life in Germany had not been too pressing and he had remained comparatively free from attacks. However, after arrival in this country he not only faced the problem of resettlement for himself and his family but was also burdened with a feeling of economic insecurity while seeking a job with decent pay. The attacks became more frequent and he had two seizures within a period of several weeks. Fatigue and emotional stress always seemed to precipitate the episodes.

The attack of palpitation initiating the admission of the patient to Queens General Hospital began on July 4, 1952, and was associated with weakness, dyspnea and

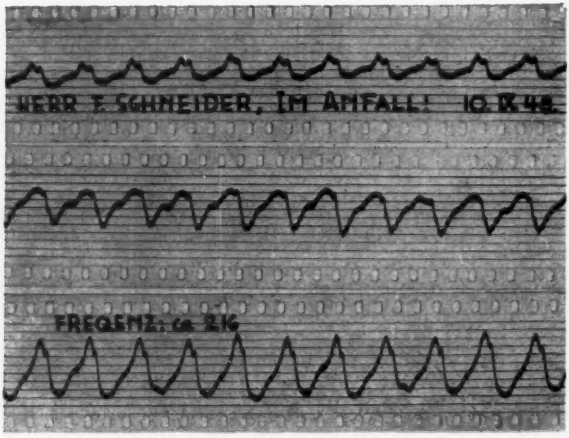

FIG. 2. Electrocardiogram taken while at Bad Nauheim, Germany, on September 10, 1948, showing paroxysm of ventricular tachycardia with cardiac rate of 216.

swelling of the ankles. For one day prior to admission the patient had noted blood-tinged sputum. He had been taking one tablet of digitalis daily for one week prior to admission.

Physical examination revealed a fairly well developed and well nourished white adult male, lying supine in bed and moderately dyspneic. The heart rate was found to be 180, and the precordial maximal impulse was 9.5 cm. from the midsternal line in the fourth intercostal space. The systolic blood pressure was 95 and the diastolic was unobtainable. There was 1 to 2 plus pitting edema of the ankles.

Electrocardiogram on admission confirmed the diagnosis of ventricular tachycardia. He was given 500 mg. of Pronestyl intravenously, followed by 500 mg. every four hours by mouth. The attack was aborted a few hours after admission, and throughout the remainder of his hospital stay he was kept on 250 mg. of Pronestyl orally three times daily.

Two days after admission the patient complained of right chest pain, and examination revealed signs of consolidation at the right base. He raised dark brown sputum, and a thoracentesis on July 26 yielded 360 c.c. of blood-tinged viscid fluid.

The diagnosis of complicating pulmonary infarction was made, and the patient was treated with anticoagulants and antibiotics. Thereafter, improvement was progressive and the patient was discharged on August 9 with the final diagnosis of paroxysmal ventricular tachycardia, complicated by pulmonary infarction.

Just 11 days later, on August 20, the patient was re-admitted to the hospital. During his brief sojourn at home he had suffered three episodes of palpitation accompanied by weakness. He returned to the hospital because of weakness and fatigue. An electrocardiogram taken during this admission showed regular sinus rhythm with premature ventricular contractions. Because of the patient's marked apprehension and nervousness, a psychiatric consultant saw him and described him as tense, anxious, and apt to "blow his top" easily. He was discharged on August 28 and referred for follow-up in the cardiology clinic as well as the mental hygiene clinic.

He was then followed in the out-patient cardiology clinic and continued on oral Pronestyl as well as phenobarbital prophylactically. In addition, psychotherapy was begun at the psychosomatic clinic of another institution. This clinic shared the opinion of the staff of Queens General Hospital that there was a close relationship between the onset of the attacks of tachycardia and disturbances in the emotional life of the patient.

On November 3 the patient was admitted to Queens General Hospital for the third time complaining of palpitation of eight hours' duration. He had returned to his job in an orthopedic appliance shop three weeks previously. On the day of admission he was breaking a new man in for his job and had been rushed. This apparently precipitated another attack of palpitation and tachycardia. Since his last discharge he had been fairly well and had suffered only occasional and brief episodes of palpitation. He had noted that with freedom from pressure his pulse rate remained slow. Examination revealed the patient to be in acute distress, with a heart rate of 286 per minute. He was given 1 gm. of Pronestyl and one unit of plasma by infusion and then continued on oral Pronestyl. The tachycardia persisted, and the patient was quite apprehensive and vomited on several occasions. The paroxysm finally broke the following day and the patient was discharged on November 5 on a régime of 250 mg. of Pronestyl four times daily.

For the next few months the patient had only brief and infrequent bouts of palpitation and tachycardia. However, on June 15, 1953, a fourth admission to Queens General Hospital was required because of another prolonged paroxysm. This, too, was finally broken after several hours with the use of both Pronestyl and quinidine. He was discharged on June 18 on a régime of 1.5 gm. of Pronestyl daily in six divided doses.

On July 27 he was admitted to Queens General Hospital for the fifth time. He had not worked from the time of his previous discharge until the day of admission. On that day he had started on a new job in a grocery store. After work he had returned home quite tired and, upon taking a deep sigh, had noted the onset of palpitation and tachycardia. Examination revealed the patient to be very apprehensive, with an apical rate of 180 and blood pressure of 86/68 mm. of Hg. Only the first heart sound was audible at the apex. This paroxysm persisted for more than two days, despite the administration of Pronestyl both parenterally and by mouth. On July 30 the tachycardia was finally broken. Successive electrocardiograms (figures 3, 4 and 5) illustrate the conversion from the ventricular tachycardia to a normal rhythm with the administration of Pronestyl. On August 6 he was again discharged to the cardiology clinic on a régime of 750 mg. of Pronestyl every four hours.

In September he had another attack, lasting three hours, and was admitted to another institution, where he remained 11 days. This attack was also terminated by intravenous Pronestyl. On discharge he was placed on quinidine, grains 3 every four hours, and oral Pronestyl was discontinued.

When last seen, on March 22, 1954, he stated he had been free of attacks since he had been placed on quinidine. He was working as a machinist's helper. He was with congenial workers for the first time in quite a period, and hence was in a much better frame of mind. His wife at that time was quite emphatic in her observation

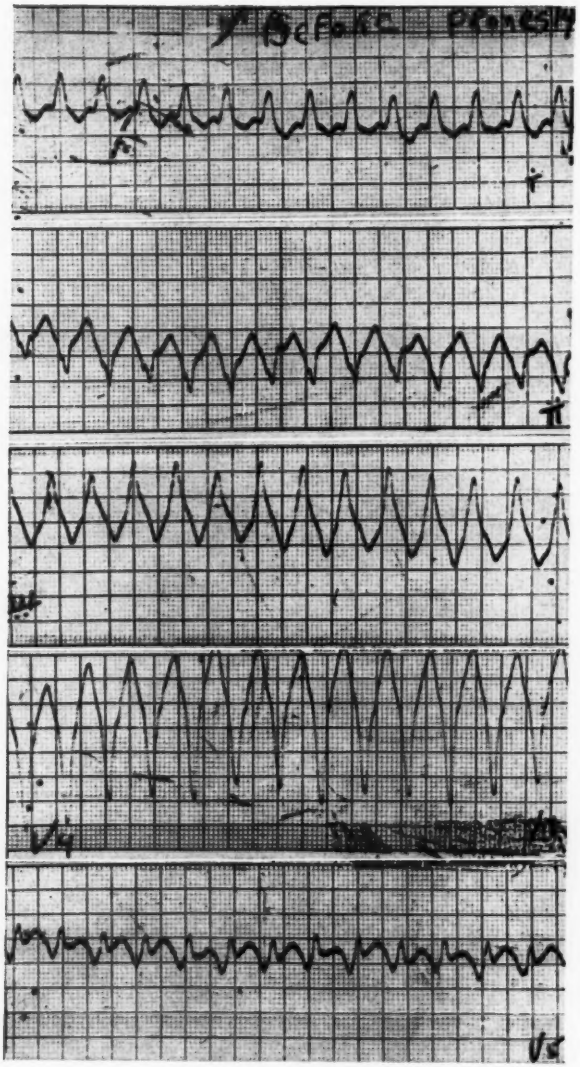

FIG. 3. Electrocardiogram taken July 30, 1953, at Queens General Hospital, illustrating ventricular tachycardia.

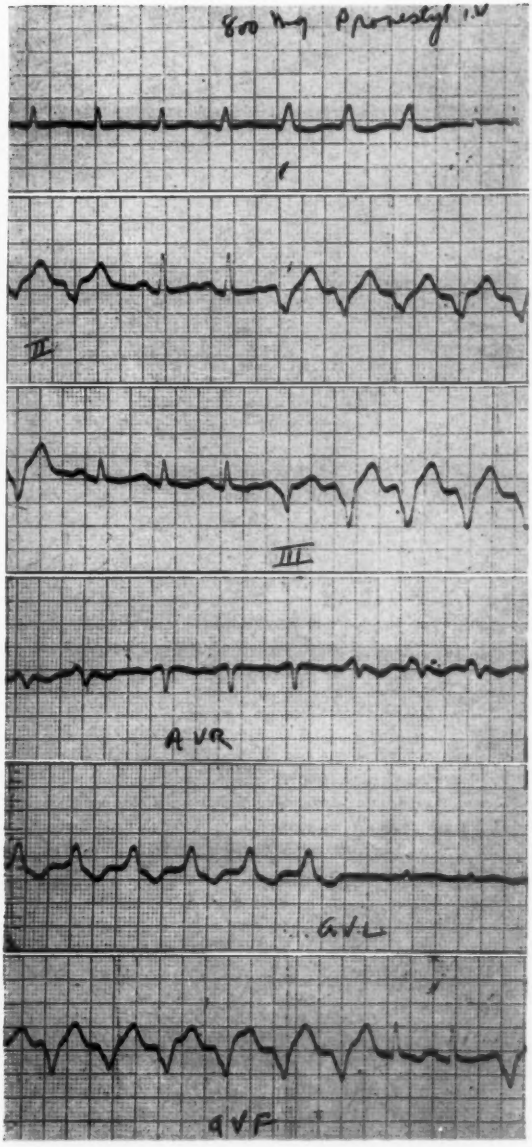

FIG. 4. Electrocardiogram after 800 mg. Pronestyl intravenously, illustrating trend to normal sinus rhythm broken by short runs of ventricular tachycardia. Taken July 30, 1953.

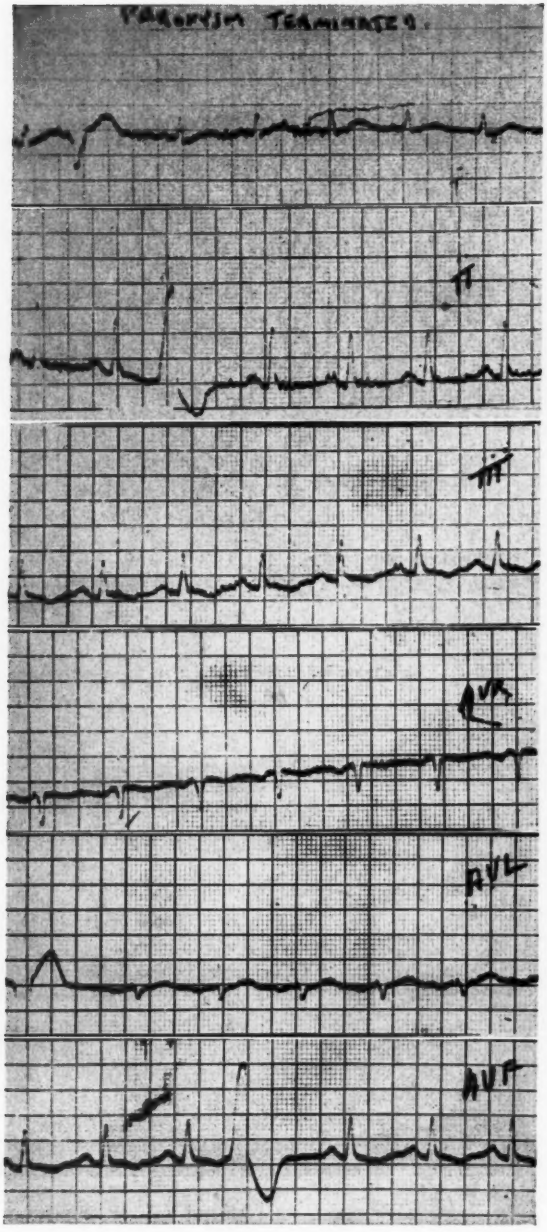

FIG. 5. Electrocardiogram on cessation of paroxysm and resumption of normal sinus rhythm on July 30, 1953. Note resemblance of extrasystoles to the configuration of the complexes during the paroxysm.

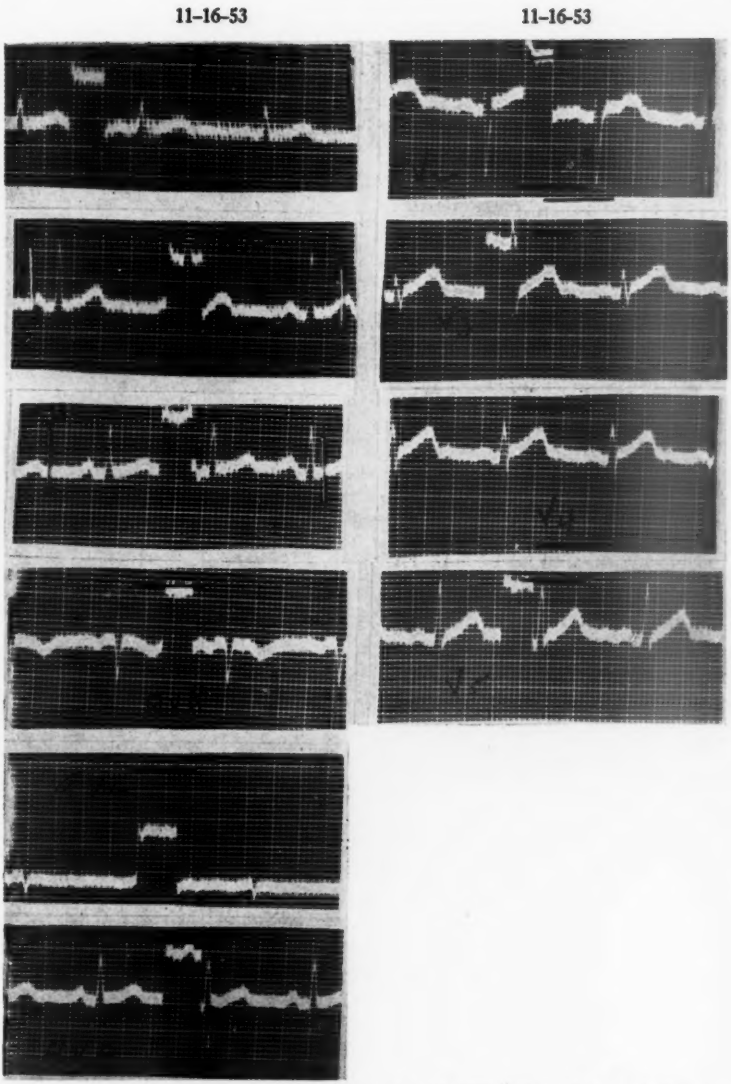

FIG. 6. Electrocardiogram taken on November 16, 1953. Normal sinus rhythm and no abnormalities.

that her husband was always much more prone to attacks when he was fatigued and under emotional strain. At this writing he has had no attack for six months, and examination of his heart reveals no abnormalities. Recent electrocardiogram (figure 6) and x-ray of chest (figure 7) reveal no cardiac abnormalities.

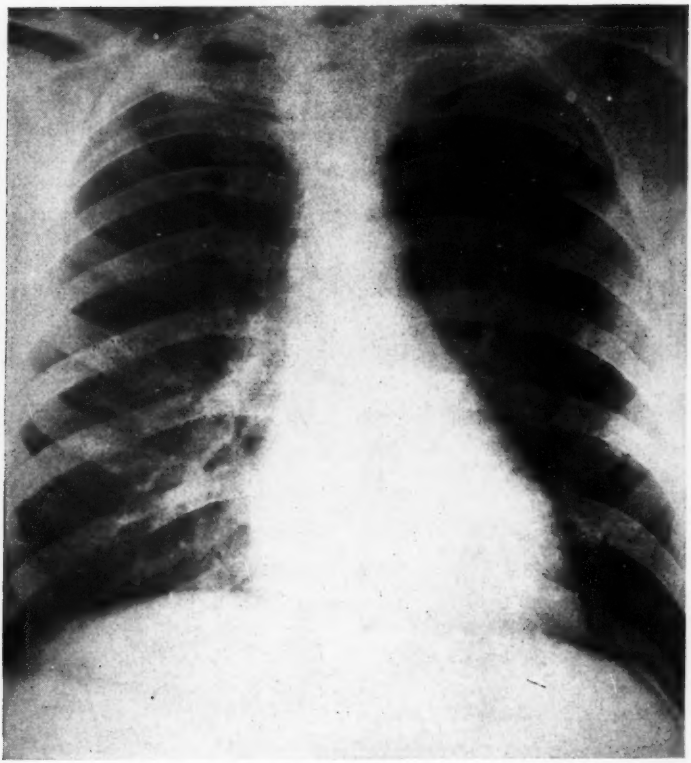

FIG. 7. X-ray of chest in November, 1953, showing heart of normal size and configuration.

DISCUSSION

The comparative rarity of paroxysmal ventricular tachycardia without demonstrable organic heart disease such as myocardial infarction or coronary artery disease has already been noted. Of course, digitalis poisoning may also be a precipitating cause, but this has been eliminated in the case herewith presented. In previously reported cases without organic heart disease, the chief causative factors have been noted as overexertion, emotional excitement and tobacco.[7, 8] Attacks without organic heart disease have even been reported on an orthostatic basis, with precipitation by excitement or mild exertion in the upright position and invariable relief by lying down.[9] All of these etiologic agents serve to increase sympathetic tone. The relationship of these factors to other types of functional heart disease, such as neurocirculatory asthenia and supraventricular tachycardia, have been known for many years.[10, 11]

Froment et al.,[12] in a recent review in the *British Heart Journal* classifying types of ventricular tachycardia, noted one grouping of "persistent and prolonged ventricular tachycardia developing in sound hearts usually in young subjects."

They estimated the age of onset in this group as commonly around 20, predominantly in men, the sex ratio being 10 men to three women. Although most of these attacks of benign ventricular tachycardia have been reported in young subjects or those in early middle age, it is interesting to note Bjerkelund's report of a case in a 10 year old boy.[13] Incidentally, in the article by Froment et al., although it is admitted that the origin of benign ventricular paroxysmal tachycardia remains a mystery, it is postulated that there may be an irritable focus in the septum and a microscopic lesion of the conducting system which does not impair the usual functioning of the heart.

In the case here reported, there has been apparently a very close relationship between the onset of attacks and periods of emotional stress and excitement. The patient is a highstrung, tense, nervous type, and during the last nine years, since the onset of his bouts of paroxysmal ventricular tachycardia, has been subjected to many pressing stresses and strains. These have been: five years in the German army during World War II, including two years at the Russian front; confinement in a prisoner-of-war camp; readjustment to a new country and associated economic insecurity; and, finally, trying to find a niche for himself in a new occupation. Although he now makes only $50.00 a week, he likes his new job, the boss and his fellow workers. He feels that his present mood of contentment explains in a large measure the absence of any attack during the past six months. During the 15 months before that, he had had six severe attacks, all requiring hospitalization. In that period he was changing jobs and felt insecure and emotionally tense. In addition, after each attack he felt anxious and despondent for two or three weeks.

It is also of considerable interest that this patient suffered at least three of the usually mentioned complications of persistent ventricular tachycardia. These were most dramatically highlighted in his first admission to Queens General Hospital in July, 1952. His tachycardia had already been of several days' duration and, after it had been broken by Pronestyl, electrocardiograms during the subsequent week revealed changes suggestive of epicardial infarction. In retrospect, these changes were undoubtedly due to subendocardial ischemia after prolonged ventricular tachycardia. This is illustrated by complete return to normal of the electrocardiogram taken only a short time later. Abnormal electrocardiograms following bouts of paroxysmal tachycardia have been noted by several authors, and are especially well illustrated in an article by Ward in 1946.[14]

Another common complication of prolonged ventricular tachycardia which occurred during this admission was evidence of congestive failure, as manifested by dyspnea, ankle edema and basal râles. Finally, with prolonged tachycardia there is also a tendency for the formation of mural thrombi, with ensuing pulmonary or systemic infarction. This patient developed a pulmonary infarction, as evidenced by hemoptysis, chest pain, bloody pleural effusion and confirming physical and x-ray findings.

As far as treatment is concerned, most authors are agreed that Pronestyl and quinidine are the best agents for the acute episode of ventricular tachycardia. In the case here reported, Pronestyl seemed to be the more effective drug, and it was given with the usual precautions, that is, slowly, and with electrocardiographic control when given intravenously.

Inasmuch as this patient has now had recurrent attacks of paroxysmal ventricular tachycardia over a period of nine years, the problem of prophylaxis

assumes particular importance. The most significant factor in prophylaxis is the exclusion of those noxious influences which apparently elevate sympathetic tone and so induce the onset of these attacks. In our case, emotional stress and fatigue seemed to be most disturbing in this regard. Hence, all that has been done to assist this patient in his emotional balance and in the diminution of stress and strains has been helpful.

As far as drugs are concerned, quinidine seems to have been of greater value prophylactically than Prŏnestyl, although the latter agent is probably more specific in the treatment of the acute attack. It is interesting to note that an adrenergic blocking agent, Dibenamine, has proved useful in the prevention of spontaneous arrhythmias, including ventricular tachycardia, following cyclopropane anesthesia.[15, 16] As noted by Master,[17] this drug deserves a clinical trial in ventricular tachycardia not precipitated by anesthesia or operative procedures.

The prognosis in cases of paroxysmal ventricular tachycardia without associated heart disease is usually good. This has been noted by several authors. It should be observed, however, that prolonged and unrelieved paroxysmal ventricular tachycardia unassociated with underlying organic heart disease may occasionally be fatal. Elliot and Fenn [18] reported such a case in a girl of 19, with death from cardiac exhaustion after an unrelieved paroxysm of 32 days. However, this is the exception. Our case is now 36 years of age and has had recurrent bouts of paroxysmal ventricular tachycardia since 1945. He still presents no evidence of cardiac damage, and his general health between paroxysms remains good.

Summary

1. A case of paroxysmal ventricular tachycardia in a man now aged 36 is reported. This patient has had recurrent attacks for the last nine years and nevertheless shows no evidence of organic heart disease. A particularly interesting feature is the apparent relationship of emotional strain and fatigue to the onset of the attacks.

Acknowledgment

Grateful appreciation is expressed to Dr. Arthur A. Fischl, Director of the Medical Service of Queens General Hospital, for his coöperation.

BIBLIOGRAPHY

1. Armbrust, C. A., and Levine, S. A.: Paroxysmal ventricular tachycardia. A study of 107 cases, Circulation **1**: 28, 1950.
2. Cooke, W. T., and White, P. D.: Paroxysmal ventricular tachycardia, Brit. Heart J. **5**: 33, 1943.
3. Williams, C., and Ellis, L. B.: Ventricular tachycardia, an analysis of 36 cases, Arch. Int. Med. **71**: 137, 1943.
4. Herrmann, G. R., and Hejtmancik, M. R.: A clinical and electrocardiographic study of paroxysmal ventricular tachycardia and its management, Ann. Int. Med. **28**: 989, 1948.
5. Lundy, C. J., and McLellan, L. L.: Paroxysmal ventricular tachycardia, an etiological study with special reference to the type, Ann. Int. Med. **7**: 812, 1934.
6. Strauss, M. B.: Paroxysmal ventricular tachycardia, Am. J. M. Sc. **179**: 337, 1930.
7. Bellet, S.: Clinical disorder of the heart beat, 1953, Lea and Febiger, Philadelphia.

8. Wilson, F. N., Wishard, S. W., MacLeod, A. G., and Barker, P. S.: A clinical type of paroxysmal tachycardia of ventricular origin in which paroxysms are induced by exertion, Am. Heart J. 8: 155, 1932.
9. Peters, M., and Penner, S. L.: Orthostatic paroxysmal ventricular tachycardia, Am. Heart J. 32: 645, 1946.
10. Weiss, S.: The interaction between emotional states and the cardiovascular system in health and in disease, Libman Anniversary Volumes, Vol. III, 1932, International Press, New York.
11. Schwab, S. I.: The heart in emotional conflicts, Am. Heart J. 2: 166, 1926.
12. Froment, R., Gallavardin, L., and Cahen, P.: Paroxysmal ventricular tachycardia, a clinical classification, Brit. Heart J. 15: 172, 1953.
13. Bjerkelund, C. J.: Benign paroxysmal ventricular tachycardia in a ten year old boy, Acta med. Scandinav. 133: 139, 1949.
14. Ward, L. S.: Abnormal electrocardiogram following recovery from paroxysmal tachycardia, Am. Heart J. 31: 645, 1946.
15. Hecht, H. H., and Anderson, R.: Influence of Dibenamine (N, N-dibenzy-β-chloroethyl-amine) in certain functions of the sympathetic nervous system in man, Am. J. Med. 3: 3, 1947.
16. Nickerson, M., and Brown, H.: Protection by Dibenamine against "spontaneous" arrhythmias occurring during cyclopropane anesthesia, Anesthesiology 12: 216, 1951.
17. Master, A. M., Moser, M., and Jaffe, H. L.: Cardiac emergencies and heart failure, 1952, Lea and Febiger, Philadelphia.
18. Elliot, A. R., and Fenn, G. K.: Long continued ventricular tachycardia; report of an unusual case, Am. Heart J. 9: 806, 1934.

GRANULOMATOUS ARTERITIS WITH MYOCARDIAL INFARCTION: A CASE REPORT WITH AUTOPSY FINDINGS*

By Alan N. Morrison, M.D., and Maurice Abitbol, M.D., *Brooklyn, N. Y.*

This disease, first described by Hutchinson in 1890 and subsequently reported by Horton, Magath and Brown [1] in 1932, has been the subject of numerous case reports. Since the report of Horton and Magath [2] in 1937, temporal arteritis has been found to be a definite clinical and pathologic entity different from polyarteritis nodosa and thromboangiitis obliterans.

The disease characteristically occurs in the older age group, 55 to 80 years, more often in females. The onset is usually with generalized headache, malaise, anorexia, low grade fever and weakness. After a variable period of time, ranging from weeks to months, pain is experienced over the superficial arteries of the scalp. The temporal arteries are mainly involved, the occipital arteries to a somewhat lesser extent. The temporal arteries have the characteristics of segmental and nodular inflammation. There may be partial or complete loss of vision, and various cerebral symptoms varying from headache to frank mental deterioration. The clinical course has been described as usually self-limited and nonfatal, lasting for from one to 20 months, and followed by complete re-

*Received for publication April 26, 1954.
From the Medical Service of Dr. E. L. Shlevin and the Department of Pathology, Dr. D. Grayzel, Attending, Jewish Hospital of Brooklyn.

covery. Occasionally residua remain, e.g., blindness and mental changes. In typical cases one notes an anemia and leukocytosis but no eosinophilia. The sedimentation rate is elevated. No microörganisms have been isolated. The characteristic pathologic findings are presented in this case report.

The therapeutic measures in the past have been resection of the inflamed artery or infiltration of the artery with procaine,[3] roentgen radiation, antihistamines, antibiotics and, more recently, steroid therapy with ACTH and cortisone.[5, 6]

Case Report

A 67 year old white male was admitted to the Jewish Hospital of Brooklyn on October 6, 1953, with the chief complaint of loss of vision and severe headaches. He had been well until six weeks before admission, at which time throbbing temporal and occipital headaches appeared, with pain and tenderness over both temporal areas, increasing in severity. Twelve days before admission, while reading a newspaper, the patient noticed a film of darkness over the left outer visual field. This gradually became worse. Five days before admission, on arising from bed in the morning, he became aware of complete blindness in the right eye. He had worked as a laborer in an umbrella factory, but stopped seven months before admission because of weakness. His past history reveals that he had had hypertension for many years and had been treated for congestive heart failure with digitalis; he had worn a hearing aid for 30 years.

In the hospital the patient had a low grade fever up to 100.6° F. and complained of moderate headache and expressed anxiety about his failing vision. Both temporal arteries were tortuous, beaded and nonpulsating. They were now nontender, whereas the patient had previously complained of pain. The eyes revealed pale conjunctivae and sclerae. The pupils were round, regular and equal. The right pupil did not react to light, but did react consensually. Funduscopy revealed bilateral optic atrophy, with contracted arterioles and dilated veins. The right retinal arteries were bloodless. Vision was completely absent in the right eye, and only light perception over the nasal visual field was present in the left eye. The facial arteries were palpable but pulseless. Examination of the lungs revealed some moist râles at the left base, clearing on cough. The heart was clinically enlarged. The point of maximal impulse was seen in the sixth intercostal space, in the anterior axillary line. A grade III rough apical systolic murmur and occasional premature systoles were present. The extremities revealed absence of both dorsalis pedis and posterior tibial artery pulsations. The blood pressure was 148/76 mm. of Hg, and the temperature was 99.4° F. The red blood count was 3.12 millions, and the hemoglobin 9 gm.%. The white blood count was 5,800, with 61 polymorphonuclears, 34 lymphocytes and 5 monocytes. The smear showed hypochromia and anisocytosis. The sedimentation rate was 61 mm./hour. The urine was normal and the Mazzini test negative. The electrocardiogram on admission revealed myocardial damage. X-ray examination of the skull was normal. The chest film showed ventricular enlargement with calcification of the aortic arch; the legs showed calcification of the arteries. The electroencephalogram was normal. Biopsy of a 1 cm. section of the right temporal artery revealed arteriosclerosis, calcification and an organized thrombus.

In the hospital the patient had a low grade fever up to 100.6° F and complained of pain in the jaw while eating; the headache was diminishing in severity, but still required codeine and aspirin for relief. In spite of the negative biopsy findings, the diagnosis of temporal arteritis was entertained in view of the clinical features, and cortisone therapy was instituted. Only 50 mg. per day were given, in view of the history of congestive failure and electrocardiographic evidence of myocardial

FIG. 1. Low power magnification (×120) of section of left anterior descending coronary artery showing the inflammatory process of granulomatous arteritis.

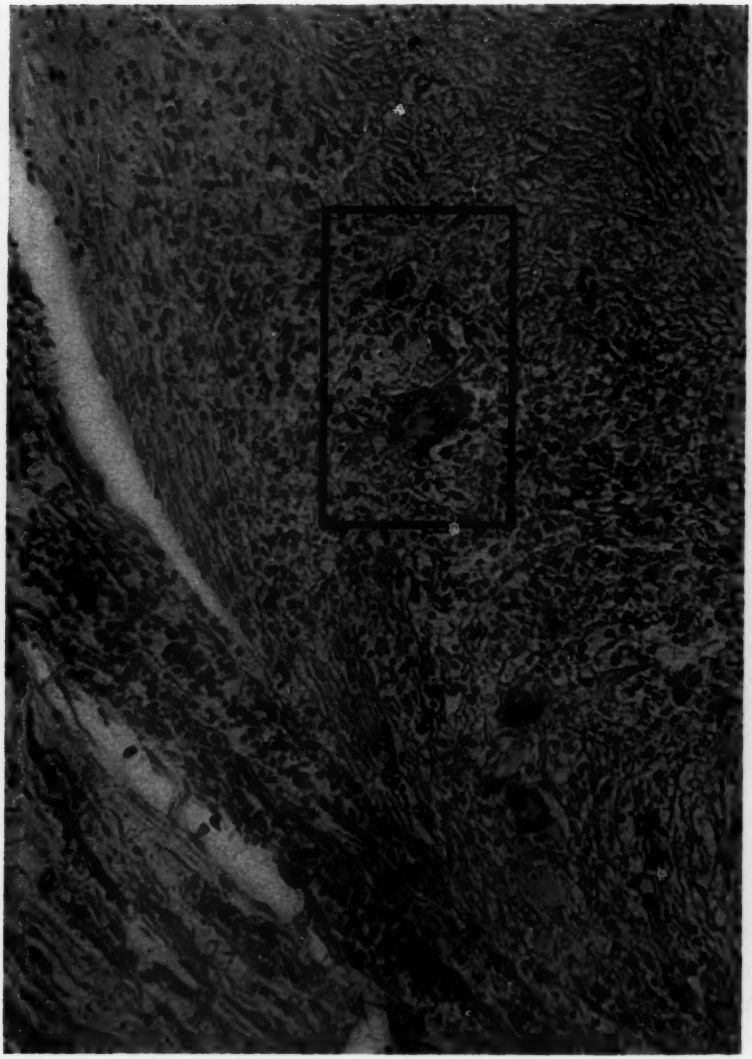

FIG. 2. Higher magnification (×300) of figure 1.

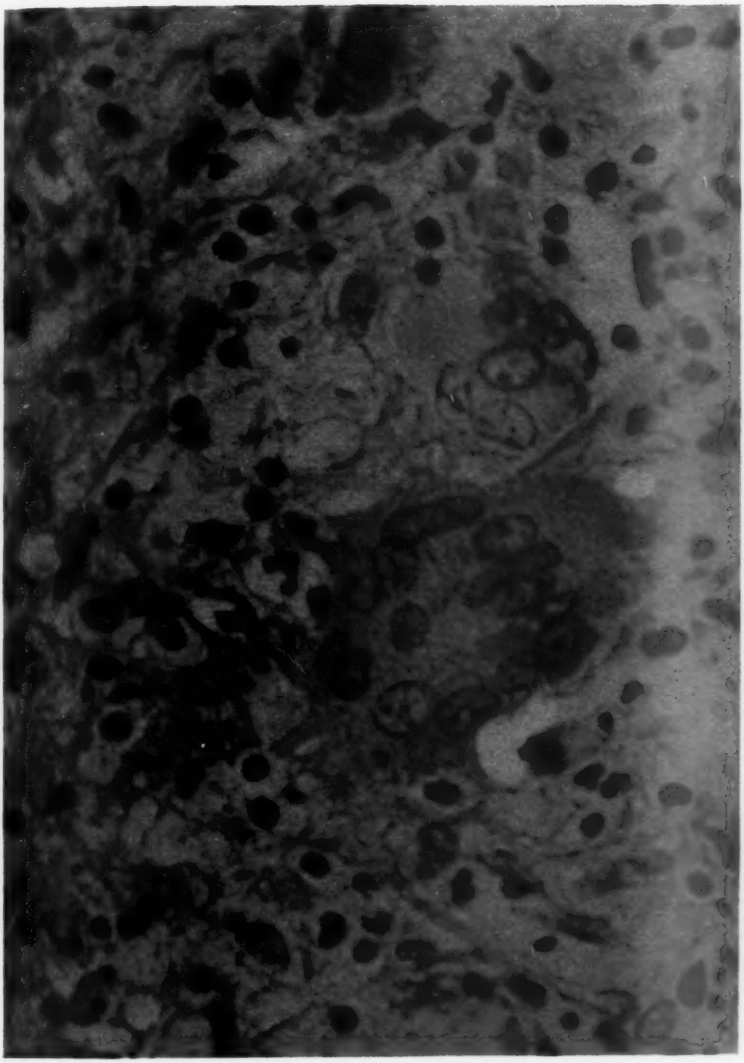

FIG. 3. High power (× 500) of marked off area of figure 2, showing foreign body type giant cells.

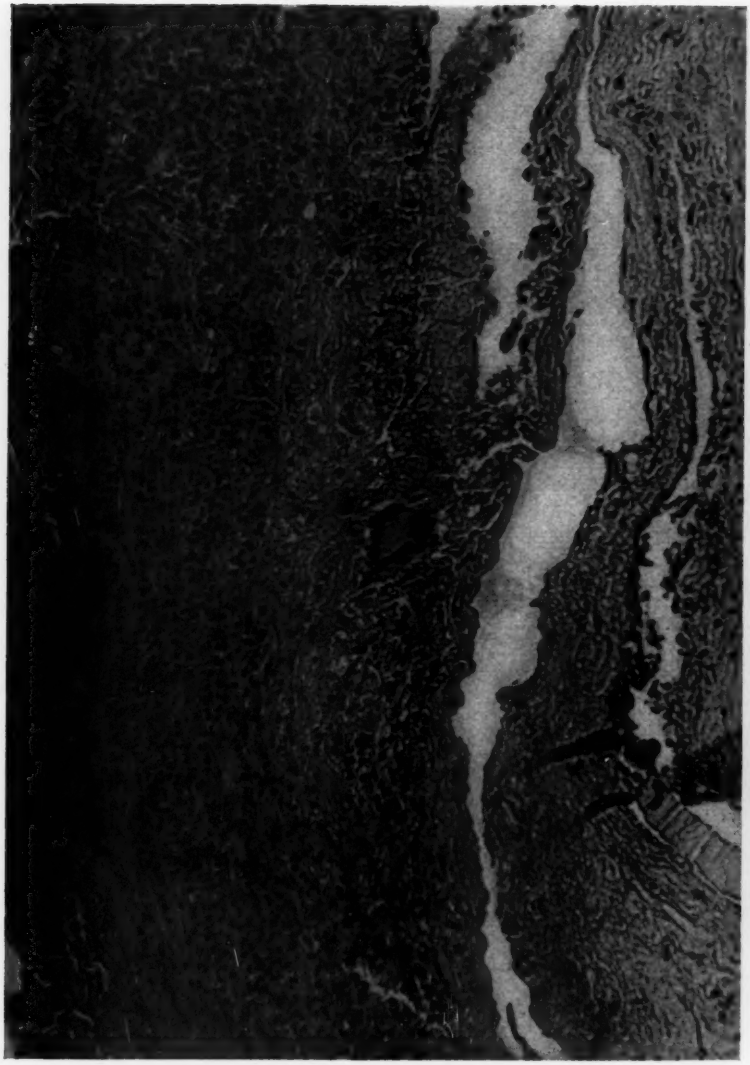

FIG. 4. Photomicrograph (× 300) showing granulomatous arteritis of the basilar artery.

FIG. 4. Photomicrograph (× 300) showing granulomatous arteritis of the basilar artery.

FIG. 5. Photomicrograph (× 300) of the right ophthalmic artery showing the inflammatory process and obliteration of the lumen.

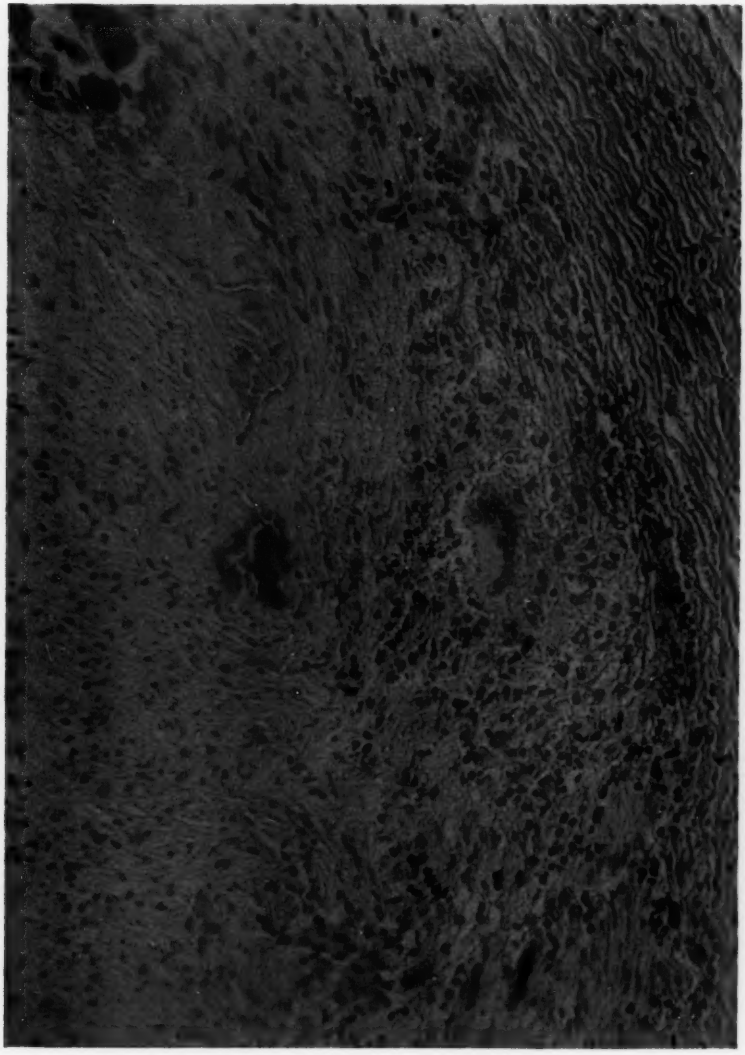

FIG. 6. Photomicrograph of the left temporal artery (×30)) showing association of arteriosclerosis and granulomatous arteritis with giant cells.

damage. The headaches disappeared and cortisone therapy was stopped three weeks later. However, there was no improvement in vision. Prior to a contemplated discharge from the hospital the patient was transfused with 500 c.c. of blood because of the persistent anemia. One hour after the transfusion the patient developed pulmonary edema. The electrocardiogram showed changes suggestive of an acute anteroseptal infarction. Despite all therapy the patient died five weeks after admission.

On autopsy the main findings were a granulomatous arteritis involving the temporal and ophthalmic arteries, all the arteries of the base of the brain and the coronaries. These arteries showed the following general features: All the layers were infiltrated with lymphocytes; the intima was markedly thickened by hyaline fibrous tissue, with narrowing or occlusion of the lumen; the media, in addition to calcification and hyaline changes, showed focal necrosis and foreign body type giant cells; the adventitia was markedly thickened by fibrous connective tissue. None of the sections showed eosinophilia.

The following arteries showed additional features:

1. The right temporal artery also showed an inflammatory reaction in the surrounding tissue secondary to the operative procedure (biopsy).
2. Both ophthalmic arteries showed a marked endothelial proliferation, occluding the right lumen and narrowing the left one.
3. All the arteries of the base of the brain (basilar, posterior, middle and anterior cerebral) showed atherosclerosis and changes of granulomatous arteritis.
4. The coronary arteries showed, in addition to the granulomatous arteritis, a moderate arteriosclerosis.

The heart was hypertrophied and dilated and weighed 600 gm. The coronary arteries were narrow but patent. On the anterior wall there was a recent subendocardial infarction. There was also evidence of myofibrosis cordis. Other findings were aneurysms of the abdominal aorta and right iliac artery, a papillary adenoma of the right kidney with a large organized hematoma, adenomatous hyperplasia of both adrenal cortices and chronic passive congestion of the lungs and liver. The brain was small, weighing 1,150 gm., and showed atrophy microscopically. Generalized arteriosclerosis was present. Arterioles of different organs showed no features of note. No specimens were taken from arteries of the limbs.

Discussion

It is widely agreed [8, 9, 10] that temporal arteritis is a generalized granulomatous, inflammatory process which has been reported to involve not only the temporal arteries but also almost every artery of the body. The term "granulomatous arteritis," proposed by Meneely and Bigelow,[10] appears to be more inclusive. Until now the most serious complication of this disease has been some degree of visual loss in about one third of all cases. Temporal arteritis per se is not a lethal disease.

In this case the cause of death was a recent anterior wall myocardial infarction. The coronary arteries, however, showed the characteristic histologic picture of granulomatous arteritis with multinucleated giant cells. Angina pectoris associated with temporal arteritis has been reported by Cole.[4b] Another case, reported by Cooke et al.,[9] showed coronary arteritis without myocardial infarction. Kaye [11] reported seven cases of temporal arteritis, one of which was complicated by pericarditis, with an audible friction rub, confirmed by electrocardiogram, which subsided completely. In view of the patency of the coronary vessels in the present case, and in view of the inflammatory process, one may

postulate the possibility of spasm of the coronary arteries as responsible for the infarct of the heart; the transfusion which the patient received most likely contributed to the cardiac failure. In view of the generalized nature of this disease, cortisone would appear preferable to temporal artery resection and procaine infiltration. It is important to realize that the temporal arteries may be segmentally involved and, unless an adequate length is removed at biopsy, the early pathologic diagnosis may be missed, as occurred in this case. Fifty milligrams of cortisone daily relieved the headaches completely, but the granulomatous inflammatory process in the arteries persisted. It is our belief that larger doses of cortisone should be employed in those cases without cardiac manifestations.

At the present time biopsy is necessary to confirm the diagnosis, and the temporal artery, being superficial and expendable, makes this the ideal site for biopsy. It is possible that granulomatous arteritis of the type described here may occur more frequently, but it can be elusive in the absence of temporal artery involvement.

Summary

1. A case of granulomatous arteritis, temporal arteritis type, is reported.

2. Similar involvement of the cranial, ophthalmic and coronary arteries occurred.

3. Biopsy of the temporal artery usually confirms the diagnosis, but because of the segmental involvement the histopathologic features may be missed.

4. There is no specific therapy. Cortisone appears to be worthy of trial.

5. This is the first case reported in the literature of a myocardial infarction due to pathologically demonstrated granulomatous arteritis.

BIBLIOGRAPHY

1. Horton, B. T., Magath, T. B., and Brown, G. E.: An undescribed form of arteritis of the temporal vessels, Proc. Staff Meet., Mayo Clin. **7**: 700, 1932.
2. Horton, B. T., and Magath, T. B.: Arteritis of the temporal vessels; report of seven cases, Proc. Staff Meet., Mayo Clin. **12**: 548, 1937.
3. Roberts, A. M., and Askey, J. M.: Temporal arteritis, J. A. M. A. **137**: 697, 1948.
4. (a) Kristensen, H. P. O.: A case of temporal arteritis treated with ACTH, Acta med. Scandinav. **142**: 591, 1952.
   (b) Cole, L., cited by Kristensen.[4a]
5. Schulman, S., and Bergenstal, D.: Treatment of temporal arteritis with cortisone. A case report, Ann. Int. Med. **37**: 1088, 1952.
6. Shick, R. M., Baggenstoss, A. H., Fuller, B. F., and Polley, H. F.: Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis, Proc. Staff Meet., Mayo Clin. **25**: 492, 1950.
7. Tate, W. M., and Wheeler, J. A.: Temporal arteritis. Report of a case with ACTH therapy, J. Kansas M. Soc. **52**: 374, 1951.
8. Sprague, P. H., and MacKenzie, W. C.: A case of temporal arteritis, Canad. M. A. J. **43**: 562, 1940.
9. Cooke, W. T., Cloake, P. C., Govan, A. D., and Colbeck, J.: Temporal arteritis: a generalized vascular disease, Quart. J. Med. **39**: 47, 1946.
10. Meneely, J. K., and Bigelow, N. H.: Temporal arteritis. A critical evaluation of this disorder, Am. J. Med. **14**: 46, 1953.
11. Kaye, S. L.: Temporal arteritis; report of seven cases, Lancet **1**: 1039, 1949.

JAUNDICE DURING METHIMAZOLE ("TAPAZOLE") ADMINISTRATION *

By JOSEPH C. SHIPP, M.D.,† *New York, N. Y.*

METHIMAZOLE, a highly effective antithyroid agent introduced by Stanley and Astwood [1] in 1949, is being used with increasing frequency in the treatment of hyperthyroidism. Toxic reactions have occurred in approximately 5% of over 200 reported cases.[2, 3, 4, 5] These include fever, skin rashes and bone marrow depression. Jaundice has been observed during the course of methimazole therapy. There have been few instances with adequate documentation of the histologic changes responsible for the alterations in hepatic function. Specht and Boehme [6] called attention to an obstruction-type jaundice associated with a fatal agranulocytic reaction which occurred one month after the initiation of methimazole therapy. Histologically, the liver was described as showing "central lobular congestion."

The following case is an example of jaundice occurring during the administration of methimazole. Liver biopsy permitted a demonstration of the pathologic changes responsible for the jaundice.

CASE REPORT

The patient, a 63 year old Austrian-born white female, was admitted to the Presbyterian Hospital for the first time on January 28, 1953, because of symptoms of hyperthyroidism and congestive heart failure of 10 months' duration. An asymptomatic goiter had been present for over 25 years. A recent cholecystogram and an x-ray examination of the upper gastrointestinal tract were normal. Severe "growing pains" were present from age 10 to age 14; other stigmata of rheumatic fever or cardiac abnormalities were denied. The past and family history was otherwise noncontributory.

The admission physical examination revealed a temperature of 99° F., an irregular pulse of 84, and a blood pressure of 150/60 mm. of Hg. There was a fine tremor of the hands. The eyes were normal. The right vocal cord was paralyzed. The enlarged right lobe of the thyroid (without an associated thrill or bruit) displaced the trachea to the left. The neck veins were distended and the venous pressure was 110 mm. of saline. The lungs were clear. The heart was enlarged. There were murmurs of mitral insufficiency, aortic stenosis and aortic insufficiency. A smooth, nontender liver margin was palpable 2 cm. below the costal margin. The examination was otherwise negative.

The laboratory studies disclosed a hemoglobin of 15 gm.%, a leukocyte count of 10,000 per cubic millimeter, with a normal differential, and an erythrocyte sedimentation (Westergren) of 23 mm. per hour. Urine and stool were normal. The basal metabolic rate was plus 52%. A 24 hour thyroid uptake of 15 microcuries of radioactive iodine (I^{131}) was 28%. (The recent cholecystogram invalidates this determination.) The serum cholesterol was 232 mg.% with 151 mg.% in the esterified form. Radiographically there was a calcified retrosternal extension of the enlarged

* Received for publication August 16, 1954.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital in the City of New York.

† Present address: Department of Medicine, Harvard Medical School, Boston, Massachusetts.

thyroid, a moderate degree of generalized cardiac enlargement and pulmonary congestion. An electrocardiogram showed auricular fibrillation.

It was the clinical impression that the patient had inactive rheumatic heart disease with mitral insufficiency, aortic stenosis and aortic insufficiency, with the hyperthyroidism a significant additive factor in the production of the congestive failure.

On February 20 the patient was given 6 mc. of radioactive iodine therapeutically. A three-week course of sodium iodide (0.1 gm. daily) was started the following day. One week later the patient was even more thyrotoxic, as evidenced by a basal metabolic rate of plus 73%. Methimazole (15 mg. four times daily) was started on February 27. The congestive heart failure responded to conventional therapy.

On April 11 the patient developed itching of the scalp, followed by generalized pruritus. The pruritus was described as subsiding coincident with local therapy to the scalp for what was thought to be pediculosis. At the time of discharge, on April 17, the patient had a basal metabolic rate of plus 34% and a leukocyte count of 7,000 per cubic millimeter, with a normal differential count.

When the patient was seen in the clinic two weeks later she was overtly jaundiced and was re-admitted to the hospital. Close questioning revealed that the pruritus noted near the end of the previous admission had persisted and increased; anorexia, right upper quadrant distress, dark urine and light colored stools had been present during the previous week. She had received no transfusions or plasma during the previous hospitalization.

On physical examination she was icteric, afebrile and fibrillating at a rate of 72. A nontender liver margin was barely palpable; the spleen was not felt, and there was no abdominal tenderness. Otherwise the examination was unchanged.

Initially she had a hemoglobin of 14 gm.%, a hematocrit of 47% and a leukocyte count of 3,100 per cubic millimeter, with 36% neutrophils, 63% lymphocytes and 1% eosinophils. There were 174,000 platelets per cubic millimeter and 0.5% reticulocytes. The urine was strongly positive for bile. The acholic stool was negative for occult blood (guaiac). Liver function studies revealed a serum bilirubin of 8.7 mg.% (direct), alkaline phosphatase of 23 Bodansky units, total cholesterol of 400 mg.% with 242 mg.% esterified, serum albumin of 4.2 gm.%, serum globulin of 2.3 gm.%, normal prothrombin time and negative cephalin flocculation and thymol turbidity tests.

The methimazole was stopped. Over a seven day period the patient became febrile and disoriented and deteriorated rapidly, the leukocyte count falling to a low of 50 with complete absence of granulocytes. The degree of jaundice increased with the bilirubin, reaching a high of 27 mg.%. Coincident with penicillin, streptomycin, Terramycin, parenteral alimentation and cortisone (100 mg. daily for one week), marked symptomatic improvement occurred.

The obstructive-type jaundice gradually diminished.

Bile was first observed in the stool eight weeks after the onset of the jaundice. Two weeks later the serum bilirubin was 1.1 mg.%. The serum alkaline phosphatase remained elevated, and cephalin flocculation and thymol turbidity tests were persistently negative. A repeat x-ray examination of the upper gastrointestinal tract and cholecystogram were normal. A roentgenographic skeletal survey disclosed only generalized demineralization.

A liver biopsy on May 26 (figure 1) showed bile stasis in the centrolobular zone. There were accumulations of bile in the hepatic cells as well as in the moderately distended bile canaliculi. Minute collections of mononuclear cells were present in some of the portal areas. There was no definite hepatocellular necrosis. However, the outlines of the liver cells in the centrolobular zone were indistinct, suggesting possible degenerative changes.

A temporary thrombocytopenia, without complicating hemorrhagic manifestations, developed coincident with the agranulocytosis. A bone marrow aspirate

showed hypoplasia of all elements. An anemia developed gradually during the first month, with the hemoglobin falling from 14 to 8 gm.%. A reticulocytosis of up to 8% was associated. The direct and indirect Coombs' tests were negative, and the red blood cell osmotic fragility was normal. Repeated stool examinations were negative for occult blood (guaiac). Six blood transfusions were required to maintain a normal hematocrit.

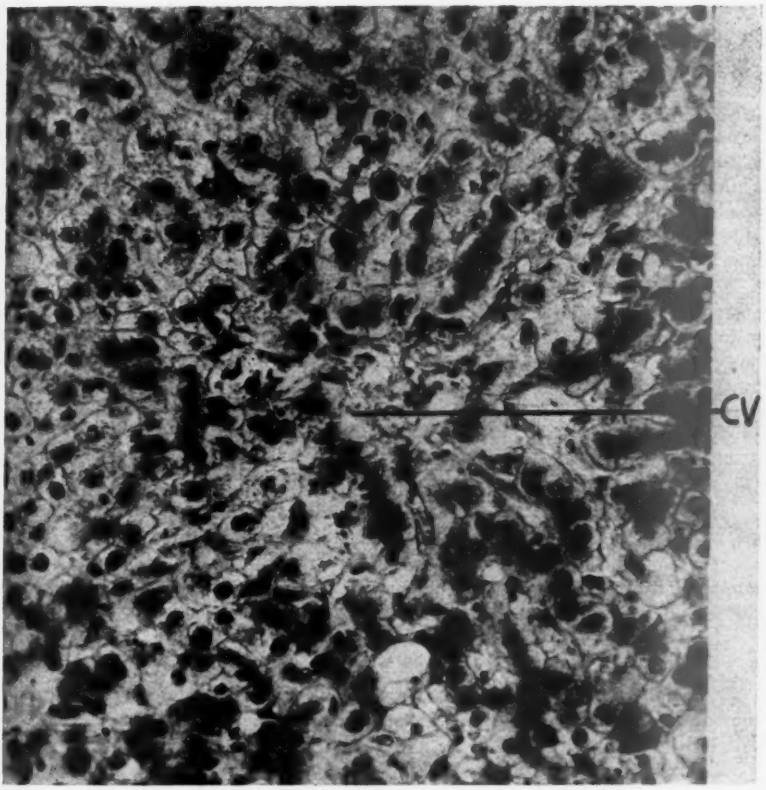

FIG. 1. Photomicrograph of the central portion of a liver lobule (needle biopsy). There are bile plugs in the biliary canaliculi around the central vein (cv). Small amounts of bile are within the hepatic cells. Note the absence of any inflammatory reaction or significant hepatocellular necrosis. (H & E—330 ×.)

With a repeat basal metabolic rate of plus 35%, a second therapeutic dose of radioactive iodine (5 mc.) was given on June 11. She was discharged three weeks later.

Four months following discharge she was entirely asymptomatic and had gained 15 pounds. The serum bilirubin was 0.4 mg.%, alkaline phosphatase 10 Bodansky units, basal metabolic rate plus 40%, and the complete blood count was normal.

Discussion

The clinical, laboratory and histologic features associated with jaundice occurring during the course of methimazole (Tapazole) therapy have been described. A definite toxic reaction to the methimazole is indicated by the associated bone marrow depression.

The outstanding disturbance is a centrolobular bile stasis. Functionally, there is failure to maintain the flow of bile through the finer biliary radicles. The negative cephalin flocculation test as well as the histologic findings indicate no significant hepatocellular necrosis.

The mechanism responsible for the bile stasis is not clear. An almost identical change has been described following the administration of methyl testosterone [7] and thiouracil.[8] The absence of any significant inflammatory reaction in the portal areas differentiates the jaundice following methimazole administration from the intrahepatic cholangiolitic obstructive jaundice attributed to arsphenamine and other drugs.[9] It is possible that the injury to the hepatic cells by the drug results in an increase in the viscosity of the bile, with inspissation in the terminal bile capillaries.

Evidence that the hepatic change represents a toxic reaction to the methimazole is indirect and, to a degree, speculative. However, the clinical and histologic features are strongly against an intercurrent viral hepatitis. The onset after several weeks of therapy, the character of the laboratory and histologic findings and the rather prolonged course are very similar to the jaundice occurring with methyl testosterone and thiouracil administration.

If the hepatic changes in this case are attributable to the drug, it seems unlikely that methimazole is a markedly hepatotoxic agent, since the reported occurrence of jaundice is rare despite widespread usage.

It is noteworthy that the clinical and laboratory findings observed in this case are indistinguishable from those seen with extrahepatic biliary obstruction. An appreciation of the possible hepatotoxicity of this and other drugs, plus a liver biopsy, will in some cases establish the site of the pathologic changes producing the jaundice. Unnecessary surgical exploration may thus be avoided.

Summary

1. An example of jaundice occurring during methimazole (Tapazole) administration is reported. Bone marrow depression followed the onset of the jaundice.

2. Liver biopsy indicated that a centrolobular bile stasis was responsible for the jaundice. The latter was obstructive in type, as evidenced by an elevation of the serum bilirubin, serum alkaline phosphatase and total serum cholesterol. The laboratory data as well as the histologic features revealed no evidence of significant hepatocellular necrosis.

3. The role of methimazole as the causative agent is discussed.

4. The hepatic changes observed in association with methimazole are compared with those seen during the administration of thiouracil, methyl testosterone and arsphenamine.

5. In some cases of obstructive jaundice occurring during the administration of methimazole, as well as other drugs, a liver biopsy will establish the basic pathology. Thus, surgical exploration may not be necessary.

Table 1

TABLE 1
Case Summary

Date	Clinical Status	Antithyroid Rx			Basal Metab. Rate %	Trans-fusions	Blood							Liver Function				Misc.
		I^{131}	NaI	Meth-imazole			Hgb.	Hct.	WBC	Neut.	Lym.	Plts.	Retics. %	Bili-rubin mg. %	Alk. P'tase B.U.*	Choles-terol Esters/ Total	Ceph. Floc.	
1953 Jan.	Hyperthyroid Heart Failure				+52		15	40	10,000	62	34					151/232		
Feb.		6 mc	x		+73													
			x	x														
Mar.			x	x														
			x	x														
Apr.	Itching Discharged			x	+34				7,000	57	39							
				x														
				x														
May 1	Jaundice (re-adm.) Leukopenia			x			14	47	3,100	36	63	174,000	0.5	8	23	242/400	neg.	
May 8							12	44	120	0	100			27	8		neg.	
May 15	Thrombocytopenia						11		3,300	30	69	18,000	0.3	19				
May 22					+54		10		6,800	56	49	96,000	5.4	10	11	138/279	neg.	Liver biopsy
May 29	Anemia						8	22	5,200			155,000	8.0	6	12			
					+35	x												
June 5						x		30	9,000	71	23	290,000	8.0	3	15			
		5 mc																
June 12								34						2	13		neg.	
June 19								30						1.6	11			
						xx												
June 26	Discharged					xx		40					7.0	1.2	9	160/260		
Nov.					+40		15	42					2.0	0.4	10			

* Bodansky units.

ACKNOWLEDGMENT

The author wishes to thank Dr. Franklin M. Hanger for his helpful comments on the hepatotoxicity of drugs, and Dr. Raffael Lattes for his interpretation of the histologic material.

BIBLIOGRAPHY

1. Stanley, M. M., and Astwood, E. B.: 1-Methyl-2-mercaptoimidazole: an antithyroid compound highly active in man, Endocrinology **44**: 588 (June) 1949.
2. Reveno, W. S., and Rosenbaum, H.: Treatment of hyperthyroidism with 1-methyl-2-mercaptoimidazole, J. A. M. A. **143**: 1407 (Aug. 19) 1950.
3. Taylor, N., Teitelbaum, M., and Large, A.: Treatment of thyrotoxicosis with methimazole, Am. J. M. Sc. **222**: 138 (Aug.) 1951.
4. Hallman, B. L., and Bondy, P. K.: Experience with methimazole in the treatment of hyperthyroidism, Am. J. Med. **11**: 724 (Dec.) 1951.
5. Beierwaltes, W. H.: 1-Methyl-2-mercaptoimidazole and 1-ethyl-2-mercaptoimidale: a clinical evaluation of two new antithyroid drugs, J. Lab. and Clin. Med. **36**: 861 (Dec.) 1950.
6. Specht, N., and Boehme, E.: Death due to agranulocytosis induced by methimazole therapy, J. A. M. A. **149**: 1010 (July 12) 1952.
7. Werner, S. C., Hanger, F. M., and Kritzler, R. A.: Jaundice during methyl testosterone therapy, Am. J. Med. **8**: 325 (Mar.) 1950.
8. Gargill, S. L., and Lesses, M. F.: Toxic reactions to thiouracil, J. A. M. A. **127**: 890 (Apr. 7) 1945.
9. Hanger, F. M., and Gutman, A. B.: Post-arsphenamine jaundice apparently due to obstruction of intrahepatic biliary tract, J. A. M. A. **115**: 263 (July 27) 1940.

FIBRINOGENOPENIA AND FIBRINOLYSIS IN ACUTE MYELOGENOUS LEUKEMIA *

By ARTHUR A. COOPERBERG, M.D., and GREGORY M. A. NEIMAN, M.D.,
Montreal, Canada

FIBRINOGENOPENIA in leukemia is a rare occurrence, according to the literature. Risak [8] reported a marked fibrinogenopenia in three patients with acute myelogenous leukemia who died of severe bleeding. He assumed an impaired production of fibrinogen as the cause of the fibrinogenopenia, but tests for fibrinolysis were not carried out in these cases.

In the case reported below a reduction in plasma fibrinogen was discovered in the course of examination of the blood. Further studies revealed the presence of a fibrinolysin, which was believed to be the cause of the fibrinogenopenia. In recent years the appearance of a fibrinolysin and fibrinogenopenia as a cause of severe hemorrhagic diathesis in a variety of conditions has gained increasing recognition.[10] This case is reported to draw attention to the fact that fibrinogenopenia due to fibrinolysis may occur in acute leukemia, and that this may be

* Received for publication April 30, 1954.
From the Department of Medicine and Hematology Laboratory, Jewish General Hospital, Montreal, Canada.

an important contributing factor to the hemorrhages and cause of death in these patients.

Case Report

A 49 year old white male was admitted because of bleeding from the gums, purpura in the skin and mucous membranes, and hematuria.

The present illness had begun with increasing fatigability during the month prior to admission. There was occasional spotting of blood on his pillow on arising, but he was not aware of the source of the bleeding until the more persistent bleeding from the gums appeared five days prior to admission. He consulted his dentist who, in turn, referred him to his physician (G. N.), because of the presence of petechiae on the soft palate and buccal mucosa. The bleeding from the gums was only temporarily controlled when packed with thrombin preparations. The hematuria and purpura did not appear until the day prior to admission.

There was no family history of a hemorrhagic diathesis. The patient was a jeweler and had no contact with myelotoxic substances. He had been taking large amounts of an antacid containing small quantities of bismuth, and Sedormid for sleeping about once weekly for a few years. There was a past history of a right renal calculus and a mild hypertension. There was no clinical evidence of liver disease.

Nine months earlier the patient had been examined by one of us (G. N.) for complaints referable to a chronic peptic ulcer. At that time the physical examination and urinalysis were normal. The results of the blood examination were then as follows: hemoglobin, 95% (14.8 gm.%); red blood cells, 5,380,000; sedimentation rate, 12 mm.; white blood cells, 8,500. The blood smear showed no evidence of any abnormality in cell type or distribution.

The physical examination revealed a well developed and well nourished male of slight pallor. The pulse was 80 per minute and regular, and the blood pressure was 165/90 mm. Hg. There was some oozing of blood from the gum around the right upper incisor. Petechiae were noted on the soft palate and buccal mucosa and over the lower extremities. There was a fading ecchymosis on the abdominal wall. There was no lymphadenopathy, and the liver and spleen were not palpable. The remainder of the physical examination was essentially normal.

About 12 hours after admission the patient suddenly developed a left hemiplegia and signs of a massive intracranial hemorrhage with progressive coma. The blood pressure rose to 230/100 mm. Hg and Cheyne-Stokes respiration appeared. He received a transfusion of 400 c.c. of whole blood and 100 mg. of vitamin K_1 intravenously but died a few hours later, less than 24 hours after admission.

Laboratory Findings: The blood was examined at this hospital two days prior to admission and again on the day of admission, and results of both examinations were essentially similar (table 1). The urine was filled with red cells. The total plasma proteins were 8.84 gm.%; nonprotein nitrogen, 34 mg.%; alkaline phosphatase, 3.91 units; fibrinogen, 78 mg.%. X-ray examination of the spine and pelvis revealed no bony lesions. A bone marrow examination revealed a hyperplastic marrow due to a marked infiltration by myelocytes and promyelocytes, indicating acute myelogenous leukemia. The possibility of Sedormid purpura was originally entertained but was excluded by the bone marrow findings.

An autopsy was performed and a massive intracerebral hemorrhage of the right temporoparietal region with rupture into the ventricular system and subarachnoid space was found. There were multiple petechiae in the skin, heart, pleura, liver capsule, kidneys and small intestine. The leukemic infiltration was limited to the bone marrow and spleen. The spleen weighed 210 gm. The liver weighed 2,050 gm., and was normal on both gross and microscopic examination. There was no evidence of the usual postmortem clots in the heart or large vessels.

Comment

When the blood was examined (table 1) the prothrombin time was found to be prolonged and only a small clot was present. This suggested a fibrinogenopenia. When the plasma was heated to 56° C. for 10 minutes to precipitate fibrinogen, very little turbidity appeared compared to a normal plasma. After centrifugation only the slightest precipitate could be detected at the bottom of the tube. A quantitative determination revealed a blood fibrinogen content of only 78 mg. %.

The blood clotted normally and was kept at 37° C. Lysis of the clot was evident at the end of four hours and was complete at the end of 24 hours. The patient died within 24 hours of admission, so, unfortunately, further studies regarding the fibrinolytic activity of his blood could not be performed. However, according to Tagnon et al.,[11] the simplest and most reliable means of detecting

Table 1

	Two Days Prior to Admission	Day of Admission	Day after Admission
Hemoglobin	68% (10.6 gm. %)	62% (9.7 gm. %)	68%
Red blood cells	3,440,000	3,370,000	3,630,000
Hematocrit	31%	31%	—
Sedimentation rate	13 mm. (cor. 2 mm.)	20 mm. (cor. 5 mm.)	—
Reticulocytes	1.3%	4.2%	—
White blood cells	3,000	3,800	4,000
Myelocytes	4%	20%	—
Metamyelocytes	2%	4%	—
Stabs	4%	3%	—
Polymorphonuclears	16%	15%	—
Lymphocytes	58%	46%	—
Monocytes	10%	8%	—
Normoblasts	6%	1%	—
Eosinophils	—	4%	—
Platelets	120,000	110,000	36,000
Coagulation time	12 min.	15 min.	—
Bleeding time	3 min.	1 min.	—
Prothrombin time (normal, 13 sec.)	19 sec.	18 sec.	—
Capillary fragility	Increased	—	—
Recalcification time	80 sec.	—	—
Lysis of clot at 37° C.	4 hrs., complete in 24 hrs.	8 hrs.	—

the presence of fibrinolysis is the dissolution of the clot within 24 hours at 37° C. Weiner et al.[14] state that clot fragmentation or dissolution may occur when the fibrinogen levels are in the range of the minimal values for hemostasis (100 to 150 mg. %), and therefore need not necessarily be due to a fibrinolysin. They offer no experimental evidence for this statement. Accordingly, the following tests of the effect of different fibrinogen levels on clot dissolution were performed.

Blood was taken from an individual whose fibrinogen content was 350 mg. %. The plasma (1 part of 0.1 molar sodium oxalate solution to 9 parts of blood) was heated to 56° C. for 10 minutes. The precipitated fibrinogen was removed by centrifugation, and the clear supernatant was used as defibrinated plasma. To 0.1 c.c. of normal plasma, different proportions of defibrinated plasma were added and allowed to clot on recalcification, as shown in table 2. These were

TABLE 2

Effect of Varying Concentrations of Fibrinogen on Clot Dissolution

Defibrinated plasma	0.2	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	—
Whole plasma	—	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2
$CaCl_2$ 0.025 M	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	0.2
Coagulation time	no clot	2	2	2	2	2	2	2½	2½	2½	2½	Partial clot				2 min.
Approximate conc. of fibrinogen mg. %	0	58	44	35	30	25	22	19	17	16	15	13	12	11	11	175
Lysis of clot after 4 days at 37° C.	—	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

kept at 37° C. for four days. In none of the tubes was there any evidence of clot dissolution. A similar test was performed to include 0.5 c.c. of washed red cells in each tube; the results are recorded in table 3. With minimal fibrinogen concentrations only a portion of the blood clotted, the rest of the blood remaining in a liquid state. Even in these tubes the minimal clot persisted during the four days. Although fibrinolysin is destroyed on heating to 56° C.,[3]

TABLE 3

Effect of Varying Concentrations of Fibrinogen and Added Red Cells on Clot Dissolution

Washed R.B.C., c.c.	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Defibrinated plasma	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4
Whole plasma	0.4	0.3	0.2	0.1	—	—	—	—	—	—	—	—
¼ Whole plasma	—	—	—	—	0.4	0.3	0.2	0.1	—	—	—	—
1/10 Whole plasma	—	—	—	—	—	—	—	—	0.4	0.3	0.2	0.1
$CaCl_2$ 0.025 M	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Coagulation time, min.	1¾	1¾	2½	3	3	3½	5	5	5	5	—	—
Size of clot	Complete						2/3	1/3	1/3	1/3	Very little clot	No clot
Approximate conc. of fibrinogen, mg. %	95	70	47	23	23	17	12	6	9	7	4	2
Lysis of clot after 4 days at 37° C.	0	0	0	0	0	0	0	0	0	0	0	—

it is of no importance in these experiments, the purpose of which was to study the effect of low fibrinogen levels on clot dissolution.

DISCUSSION

It has been known for a long time that a fibrinolytic (and antifibrinolytic) system exists in blood. However, it is only recently that it has become recognized as an important mechanism of a hemorrhagic diathesis in a variety of diseases. Thus, a fibrinolysin was found to be responsible for the bleeding tendency and fibrinogenopenia in carcinoma of the prostate with widespread metastases.[11] Similarly, following pulmonary operations,[9] burns and shock,[12] phenobarbital and methyl alcohol poisoning and severe liver disease,[2] fibrinogenopenia with fibrinolysis and death due to hemorrhage have been reported. In amniotic fluid embolism,[6] premature separation of the placenta,[4, 9, 14] and with

long-standing intra-uterine death,[7] fibrinogenopenia and fibrinolytic activity have been demonstrated. In these latter cases, however, some believe that the occurrence of the fibrinolysin is a reactive process, and that intravascular coagulation and defibrination are the primary mechanism.[14]

Normal blood contains an inactive precursor of fibrinolysin called profibrinolysin. Fibrinolysokinase is necessary to activate profibrinolysin to fibrinolysin. Inhibitors of both fibrinolysokinase and fibrinolysin are also present in the blood.[1] Thus, either an increased activation of profibrinolysin or a diminution of inhibitors may lead to increased fibrinolytic activity. Fibrinolysin destroys not only fibrin but also fibrinogen, prothrombin and Factor V.[13]

In acute leukemia, hemorrhage is an important and frequent cause of death. This is usually attributed to the thrombocytopenia which is almost always present in these cases. Yet it is common experience that not all cases have serious bleeding, even with comparable degrees of thrombocytopenia. The reason for this is unknown.[5] A fibrinogenopenia would certainly be an important contributory cause of the bleeding in such cases. It is interesting to note that all three of the cases of acute leukemia with fibrinogenopenia reported by Risak [8] died of severe hemorrhage. This was also true in our patient. The platelet count in our patient was 120,000. This is higher than the critical level at which bleeding normally occurs with thrombocytopenia (55,000 per cubic millimeter or less).[5]

There are three mechanisms whereby the plasma fibrinogen levels may be reduced: First, there may be a diminished production, and this is probably the cause in cases of congenital afibrinogenemia. Whether this mechanism may also play a role in acquired fibrinogenopenias is difficult to determine. This was the belief of the earlier workers, but they did not search for the presence of fibrinolysins.[8] Second, there is the fibrinolytic mechanism in a variety of conditions, as discussed above. Finally, intravascular defibrination may occur when thromboplastic substances get into the circulation. This is discussed by Weiner et al., who feel that it may be the mechanism of incoagulable blood in severe abruption of the placenta.[14] Most of the cases of acquired fibrinogenopenia, however, appear to be due to a fibrinolysin.

Summary and Conclusion

1. A case of acute myelogenous leukemia with fibrinogenopenia due to a fibrinolysin is reported. It is felt that this was an important contributory cause of the hemorrhagic phenomena and death in this case.

2. Evidence is presented that fibrinogenopenia per se is not a factor in clot dissolution. Thus, the presence of clot dissolution is an adequate indication of fibrinolytic activity.

3. It is likely that fibrinolysis and fibrinogenopenia are more frequently present in acute leukemia than has been recognized to date. This may explain why some cases of acute leukemia have a greater tendency to bleed than do others with otherwise simliar hematologic findings.

BIBLIOGRAPHY

1. Lewis, J. H., and Ferguson, J. H.: Studies on a proteolytic enzyme system in the blood. IV. Activation of profibrinolysin by serum fibrinolysokinase, Proc. Soc. Exper. Biol. and Med. 78: 184, 1951.

2. Lewis, J. H.: Blood clotting and allied problems, Transactions of the Fifth Conference, 1952, Josiah Macy, Jr. Foundation, New York, p. 302.
3. Macfarlane, R. G., and Biggs, R.: Fibrinolysis. Its mechanism and significance, Blood 3: 1167, 1948.
4. Moloney, W. C., Egan, W. J., and Gorman, A. J.: Acquired afibrinogenemia in pregnancy, New England J. Med. 240: 596, 1949.
5. Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood 7: 152–159, 1952.
6. Reid, D. E., Weiner, A. E., and Roby, C. C.: Intravascular clotting and afibrinogenemia, the presumptive lethal factors in the syndrome of amniotic fluid embolism, Am. J. Obst. and Gynec. 66: 465, 1953.
7. Reid, D. E., Weiner, A. E., Roby, C. C., and Diamond, L. K.: Maternal afibrinogenemia associated with long-standing intrauterine fetal death, Am. J. Obst. and Gynec. 66: 500, 1953.
8. Risak, E.: Die Fibrinopenie, Ztschr. f. klin. Med. 128: 605, 1935.
9. Soulier, J. P., Mathey, J., LeBollock, A. G., Daumet, P., and Fayet, H.: Syndromes hemorragiques mortels avec incoagulabilite totale par defibrination et avec fibrinolyse, Rev. d'hémat. 7: 30, 1952.
10. Stefanini, M.: Fibrinolysis and "fibrinolytic purpura," Blood 7: 1044, 1952.
11. Tagnon, H. J., Whitmore, W. F., Jr., and Shulman, N. R.: Fibrinolysis in metastatic cancer of the prostate, Cancer 5: 9, 1952.
12. Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L.: The occurrence of fibrinolysis in shock, with observations on the prothrombin time and the plasma fibrinogen during hemorrhagic shock, Am. J. M. Sc. 211: 88, 1946.
13. Tagnon, H. J., Shulman, P., Whitmore, W. F., and Leone, L. A.: Prostatic fibrinolysin, Am. J. Med. 15: 875, 1953.
14. Weiner, A. E., Reid, D. E., and Roby, C. C.: Incoagulable blood in severe premature separation of the placenta: a method of management, Am. J. Obst. and Gynec. 66: 475, 1953.

PERIARTERITIS NODOSA: REPORT OF A CASE WITH BRAIN INVOLVEMENT*

By ZACHARY SAGAL, M.D., F.A.C.P., *Spadra, California*

THE terminology pertaining to this condition has been the subject of much discussion, the protean nature of the disease generally commented upon, and its designation as periarteritis nodosa under scrutiny for many years past. The intensive studies of Zeek and her collaborators [24] have shown that several varieties of arterial lesions have been erroneously labeled as periarteritis (or polyarteritis) nodosa. According to her classification, the case described here is not truly one of periarteritis nodosa, lacking as it does the characteristics which she considers essential for that diagnosis, but should be labeled as one of necrotizing angiitis, subtitled hypersensitivity angiitis or perhaps allergic granulomatous angiitis, whichever category it would fit best. The title of this communication was chosen as the one still more widely known at present and as yet more readily recognizable.

*Received for publication April 17, 1954.
From the Medical Ward of Pacific State Hospital.

The literature on periarteritis nodosa is quite extensive. Excellent reviews have appeared from time to time and the reader is referred to them [1, 4, 9, 20, 24] for further information. In the latter part of the Nineteenth Century periarteritis nodosa was a pathologic curiosity unexpectedly discovered post mortem. Eventually, cases of periarteritis were reported more and more frequently, the clinical course was correlated with the autopsy findings, and occasionally a case was suspected or even recognized ante mortem. Later on, reports began to appear of cases diagnosed at the bedside. Symptom complexes were described. Even some cures were reported, and there [15, 16, 18, 19] is one of over 20 years standing.[18b]

Case Report

An 18 year old male was admitted to Pacific Colony as a mental defective (imbecile: IQ—47) on January 11, 1951. Physical examination on admission was essentially negative. There was a vague history of petit mal seizures, atypical, during the period of 1942 to 1947, for which he had received no treatment. He was often troubled with skin rashes ("itch"), considered to be due to allergy. He had had chickenpox and measles in 1942. Previous and family history was noncontributory.

Routine x-ray of the chest on January 16 disclosed evidence of marked pathologic changes in both pulmonary fields; this was interpreted by the roentgenologist as "suggestive of a possible far-advanced, highly productive pulmonary tuberculosis." He described it as "diffuse nodular infiltration throughout the greater portion of the right lung, partly sparing the extreme apex and base. There is some similar but less pronounced infiltration of the left midlung field surrounding the hilum." The patient was entirely asymptomatic and presented no chest signs on physical examination. The possibility of fungus infection was considered. Reëxamination on February 5 did not disclose much change if any in the roentgenologic appearance of the chest, and the film was considered as "probably representing a diffuse productive type of pulmonary tuberculosis." The same roentgenologic appearance and interpretation were recorded on reëxamination on March 8.

On that date the patient was transferred to the isolation ward (inactive tuberculous cases) as a case of suspected tuberculosis. His general condition was described as "active, eats well, having gained 5 lbs. in weight since admission." On March 19, in an interview with his father, it was learned that the patient had been troubled with a cough for some time prior to admission to Pacific Colony and that he, as well as everyone in the family, was x-rayed, with negative findings.

The following information was obtained from the County of Riverside Health Department: Patient was sent in because of chronic cough. X-ray examination July 20, 1950, disclosed: "There is scattered infiltration throughout the right chest from the apex to the diaphragm, characterized by fibrosis and also considerable nodulation. Rather fluffed in character. The same condition obtains upon the left but to a lesser extent. There is rather scattered infection upon the left. The origin of this is a little obscure, but it is possible it is tuberculous. It will require further study." The physical findings were negative on July 20, 1950, as well as six months later. Guinea pig inoculations from stomach washings were made July 28, 1950. Guinea pig autopsy in October, 1950, showed no evidence of growth of acid-fast bacilli.

The patient was on the tuberculosis ward from March 8, 1951, until February 21, 1952, during which time he gained 20 pounds in weight and was asymptomatic as far as pulmonary tuberculosis was concerned. All tests for tuberculosis (sputum, cultures of gastric contents, skin tests) were negative. Skin tests for coccidioidomycosis and histoplasmosis were also negative. Urine examinations, blood counts and blood proteins were all within normal range. On one occasion (March 9,

1951), the eosinophils were 3%. Erythrocyte sedimentation rate was always elevated, from 63 mm. in one hour to 40 mm. The afternoon temperature was usually about 100° F.; it was at times as high as 102° F. for one day, tapering off in two to three days to 100° F.

X-ray examinations of the chest on June 15, July 31 and October 8, 1951, did not show any significant changes. On May 9, 1952, the roentgenologic report read, in part: "It had been assumed initially that this represented a rather diffuse productive type of tuberculosis which now seems difficult to accept after such an interval, particularly with no associative clinical findings. Previously, other possibilities such as histoplasmosis, some type of fungus infection as coccidioidomycosis or moniliasis had been suggested. The typical hilar thickening of sarcoidosis is not evident."

In June, 1952, the patient was operated on for correction of strabismus, with good results. The urine then showed: albumin, 1 plus; occasional granular cast, red blood cell and white blood cell. In November, 1952, he had a mild attack of infectious hepatitis (during a mild epidemic at Pacific Colony), with no complications. Aside from this illness, he was quite well from the time of discharge from the isolation ward until shortly before his admission to the medical ward on March 19, 1953. Early in February, 1953, he complained of pain in the lower part of the left leg and of a skin rash, which was considered as allergic in nature and was treated with antihistaminic drugs. X-ray examinations February 5 and February 13, 1953, showed some diffuse tissue swelling but no bone changes. A leukocyte count on February 19 showed 21,300 white blood cells, of which 73% were polymorphonuclears, 3% eosinophils, 15% lymphocytes and 9% monocytes.

On March 19 he was transferred to the medical ward because of fever (103° F.), chills and cough. There was a rash on the right foot, already fading consequent to the use of an antihistaminic. Aside from a large liver, two fingerbreadths below the costal margin, and a large spleen, four fingerbreadths below the costal margin, the physical examination was essentially negative. The café au lait tint to the skin was said to be his usual complexion. The blood pressure was 160/52 mm. of Hg. Urine: 1.020; acid; albumin, 4 plus; glucose, negative; bile, negative; many hyaline and granular casts; loaded with red blood cells; white blood cells, 10 to 15 per high power field. Hemoglobin and red blood cells were within normal range, as were the white blood cells and differential. Bleeding time, 2 minutes; clotting time, 4½ minutes. Sedimentation rate, 60 mm. in one hour. Total eosinophils, 133 per cubic millimeter. Sputum was negative for acid-fast bacilli. Histoplasmin skin test was negative. Phenolsulfonphthalein kidney function test: Dye appeared in 6 minutes. Elimination: first 15 minutes, 6%; second 15 minutes, 15%; next 30 minutes, 14%; total, first hour, 35%; second hour, another 8%. Urea nitrogen, 24.6 mg.% (March 25); creatinine, 1.6 mg.%. Blood culture, negative; electrocardiogram left ventricular strain.

X-ray of the chest on March 19 did not differ from those taken previously. The last x-ray of the chest was done on April 15, 1953. The report read: "Fine nodular densities which are rather soft in character are again noted scattered throughout both lung fields. The appearance is unchanged from 3.19.53. The picture is not inconsistent with a clinical diagnosis of periarteritis nodosa." X-ray examinations of the feet in February, 1953, and of the hands on March 27, 1953, were essentially negative: "No changes relative to possible cystic lesions of sarcoid are identified."

The patient ran a febrile course on the medical ward for only four days. The temperature after that was irregular; however, it rarely rose above 101° F., and that usually when the patient was off antibiotic or hormonal medication. For the first two weeks prior to receiving cortisone he had had frequent urticarial eruptions on upper and lower extremities, which would clear in a few hours with or without antihistaminic medication. He received penicillin, 300,000 units daily for 10 days;

streptomycin, 1 gm. daily for 10 days; aspirin, 10 gr. three times a day for pain in the right thigh, of which he complained for a few days; also phenobarbital as required. Beginning March 23 he was put on cortisone, 100 mg. a day. The temperature promptly came down to 97.5° F. for two days, then became stabilized at 99° to 100°. The liver receded so that it was barely felt, the spleen seemed smaller, and the blood pressure came down to 130/80 mm. of Hg. However, he was developing a moon face and some ankle edema, and he had gained weight. The cortisone was discontinued on March 29, as was all other medication, and he was put through various kidney and liver tests. Daily urine examinations consistently showed 4 plus albumin (12.5 gm. excreted in 24 hours), and the urine was loaded with red blood cells and casts of all kinds, including waxy casts. Mosenthal's test showed good concentration (to 1.024 maximum). Bromsulphalein, 40% retained in 5 minutes, 5% in 30 minutes. Blood albumin, 4 gm.; globulin, 3.6 gm.; cholesterol, 178 mg.%; cephalin flocculation, 1 plus in 24 hours. Thymol turbidity, 3 units. On April 3 he again developed extensive urticaria over upper and lower extremities. He complained of pain first in the right, then in the left popliteal spaces, and a petechial rash appeared over the lower part of the legs which disappeared the next day. There was similar occurrence on April 21, when a dermatologic consultation was asked for. No medication was given or used. The rash was gone the next day when the consultant came to see him. On April 7 he again had a giant urticarial rash on the left arm, with many papular elevations, all disappearing within an hour without any medication. He was otherwise asymptomatic. In general, throughout his illness, up to the last week, he did not look at all ill and kept asking to be sent back to his cottage. On April 13 the temperature was 101.4° F.; pulse, 120; there were crepitant râles in the left chest, the liver and spleen were again much enlarged, and a petechial rash appeared about the ankles. The temperature had been slowly rising for about a week prior to that. Cortisone was resumed, 200 mg. per day for three days, then 100 mg. per day. The fever dropped to normal within 48 hours, and on April 17 the liver was no longer palpable. On April 20 periorbital edema and edema about the ankles were noted; the blood pressure was 202/116 mm. of Hg, and cortisone was discontinued. The moon-shaped face and weight increase were other secondary effects of the hormonal therapy. The temperature remained normal for several days, then slowly rose to 100° F. The blood pressure dropped to 172/70 mm. of Hg by April 26, when his weight was 130 pounds. Blood proteins: albumin, 3.4 gm.%; globulin, 2.5 gm.%. On April 24 he had two convulsive seizures within a short time. It was difficult to evaluate the nature of the convulsions. The cortisone had been discontinued three days before and could hardly have been the cause of the cerebral edema. There was a history of seizures between 1942 and 1947. However, with kidney function as poor as it had been right along, uremia seemed the most likely cause to be considered. Urea nitrogen was found to be 32 mg.%; nonprotein nitrogen, 84 mg.%; creatinine, 2.96 mg.%. He complained of headaches and was very drowsy; he refused food but responded to questions. He was given 50% glucose by vein, potassium and calcium by mouth. On April 28 and 29 there was persistent vomiting of all food taken. Blood pressure rose to 212 systolic. There was gross hematuria for one day. Drowsiness became progressively more marked. On May 3, at about midnight, he had several involuntary bowel movements and became very noisy, requiring sedation. Toward morning he became disoriented and got out of bed. There were increasing dyspnea and cyanosis. He was placed in an oxygen tent, but developed pulmonary edema, and Cheyne-Stokes breathing, did not respond to any measures taken, and died.

Biopsy of skin and muscle of the left calf and of the skin about the right ankle was negative for evidence of periarteritis nodosa.

The clinical diagnosis was: periarteritis nodosa, glomerulonephritis, uremia, terminal pulmonary edema, mental deficiency.

Autopsy Findings: The autopsy was performed by Dr. D. S. Shillam, Pathologist, Pomona Valley Community Hospital. The positive findings follow:

The right lung weighed 750 gm. and the left lung 870 gm. Beneath the pleural surfaces were numerous white scars, 1 to 3 mm. in diameter, over all lobes. Hardly an area more than 2 square millimeters in diameter was uninvolved. Section surfaces through all lobes of the lungs showed profound edema, and focal areas of fibrous thickening less than 1 cm. in maximal diameter were present throughout all lobes at frequent intervals, centering principally about small blood vessels and small bronchioles. There was no gross evidence of pneumonia or consolidation. Other than edema fluids, the tracheobronchial tree showed nothing of interest.

The heart weighed 360 gm. and appeared moderately larger than normal. All the ventricles appeared slightly distended, most markedly the right.

The liver weighed 1,840 gm. and showed on section surfaces a faint yellow-tan and yellow mottling in areas up to 1 cm. in diameter, not definitely associated with any lobular pattern. The edges of the liver were rounded and the parenchyma crushed with normal resistance.

The spleen weighed 400 gm. and was two and one-half times normal size. Beneath the capsular surface were numerous opaque white scars up to 5 mm. in diameter. Sections through the spleen showed numerous similar foci some as much as 11 mm. in diameter scattered throughout the pulp. The remainder of the firm, dark red pulp showed no noteworthy gross changes.

The lymph nodes in the tracheobronchial, periaortic, pelvic and periportal chains were markedly enlarged, swollen and granular, some measuring as much as 8 cm. long and up to 2.5 cm. in external diameter. The capsules appeared intact, and there was no fusion of nodes.

The kidneys together weighed 300 gm. and were similar in size and appearance. Section surfaces showed light yellow foci in the pyramidal striations. The cortices appeared slightly granular, and the architectural markings were somewhat blurred. The capsules stripped with slight difficulty, leaving finely granular surfaces.

Microscopic: Sections of lung from several areas showed a fulminating bronchopneumonia with the alveoli in large fields filled with protein precipitate, erythrocytes and leukocytes, fibrin and macrophages in varying proportions. Terminal bronchioles were filled with exudate, and there was ulceration of inner surfaces in many areas. Focal areas of fibrosis were present throughout the lungs and, in addition, one saw in the interstitial connective tissue, most often in the peribronchial spaces, small granulomatous areas composed of lymphocytes, a few epithelioid cells and groups of giant cells, sometimes resembling foreign body structures and in other areas being quite suggestive of Langhans' cells. Within the giant cells there was foamy vacuolization of the cytoplasm in small foci; occasionally, after a considerable search, an asteroid body was seen. Occasionally one saw tubercle-like areas composed only of epithelioid cells, with a narrow rim of lymphoid tissue in the periphery. The lesions bore no relation to blood vessels. The arteries and arterioles within the lungs showed no noteworthy changes. Acid-fast stains revealed no typical tubercle bacilli.

Sections of liver showed some granularity of the cytoplasm of the hepatic cells and slight swelling. A few lymphocytes were present in the periportal spaces; occasionally one saw irregular patches of fibrous tissue showing at their periphery epithelioid nodules and granulomas similar to those described in the lung. In several sections small arterioles showed extensive fibrinoid necrosis involving the entire thickness of the wall. There was a proliferation of intimal lining cells. A few chronic inflammatory cells and a rare eosinophil were present at the periphery.

Sections of spleen showed large areas of fibrosis in which fibrosed granulomatous nodules and, in addition, more acute lesions were observed. Within the spleen the walls of quite large arteries were almost completely fibrosed. A rim of fibrinoid change was present in the outer layers of the intima and a marked intimal

proliferation of fibroblasts and intimal cells was seen. Other similar foci apparently represented previous blood vessels, in which the center showed extensive hemorrhage and occasionally some of the giant cells noted in those granulomatous lesions which elsewhere were not associated with blood vessels. Rarely, a marked fibrinoid intimal degeneration and focal patches of fibrinoid degeneration in the adventitia were seen in the smaller blood vessels. In addition, within the splenic pulp appeared granulocytes in varying stages of immaturity, and occasionally cells which appeared to be nucleated red cells.

Sections of the kidneys showed numerous abnormal glomeruli in varying stages of fibrosis. Almost all of the glomeruli showed some increase in connective tissue. In many there was a proliferation of fibroblasts in Bowman's capsule and a formation of fibrous and epithelial crescents. Many glomeruli were completely hyalinized. There were a diffuse interstitial fibrosis and infiltration of the interstitial tissues by a moderate number of chronic inflammatory cells. Many of the tubules showed marked dilatation, while others showed early atrophy. In the distal convoluted tubules and in the terminal collecting tubules numerous hyaline casts were present. Some large renal failure casts were seen in the terminal branches. In many sections deposition of calcium was seen in the epithelium and in the surrounding tissue of collecting tubules. Some of the glomeruli showed fibrous thickening of the papillary tufts forming ringlike structures, but special stains showed no collagen and no fibrinoid material deposited in these areas. Throughout a number of sections of kidney a few small arteries, apparently branches of interlobular arteries, were identified which showed marked fibrinoid necrosis involving principally the inner coats, sometimes sparing the outer layers of the muscularis. In the lesions found the entire circumference of the artery was involved. All appeared in the same stage of necrosis. No aneurysms and no healed lesions recognizable as such were identified. Some of the lesions showed infiltration of the walls by leukocytes including moderate numbers of eosinophils. Other lesions showing just as severe fibrinoid necrosis showed only lymphocytes in the walls. The large blood vessels occasionally showed slight intimal and fibrous thickening. The glomerular arterioles showed no significant changes.

Anatomic Diagnosis: Chronic glomerulonephritis. Generalized edema. Marked pulmonary edema. Extensive bronchopneumonia. Undiagnosed chronic granuloma of lungs, spleen, mediastinal lymph nodes. Acute arteritis of kidneys, spleen, liver. Nephrocalcinosis (uremic alkalosis). Mental deficiency.

The brain was examined by Dr. N. Malamud, Neuropathologist, Langley Porter Clinic, and was reported as follows:

Gross Report: The brain weighed 1,400 gm. following fixation. It was a large brain, apparently due largely to acute swelling, as evidenced by flattening of the convolutions and diffuse areas of softened consistency. There was also some evidence of an underlying malformation because of such signs as disproportion in relative size of the lobes, the occipital, frontal and temporal areas being unusually small. The basal arteries and the leptomeninges were not remarkable.

Coronal sections revealed an edematous and somewhat friable brain tissue, and numerous petechial hemorrhages, largely confined to the cerebral cortex and the caudate nuclei. A few were also seen in the cerebellar cortex. The gray matter in general appeared pale and edematous. There was also some indication of malformation in the convolutional pattern because of the increased width of the cortex, although this may have been partly explained by acute swelling.

Microscopic Report: The small meningeal and intracerebral arterioles and capillaries frequently showed changes varying from a chronic subintimal fibrous proliferation to an acute fibrinoid necrosis which pervaded almost the entire wall. Little was seen of any perivascular infiltration, but the adventitia was frequently

proliferated. There were no chronic lesions in the brain tissue, but there were multiple acute changes, predominantly in the cortex, in the form of petechial hemorrhages and/or miliary infarcts in which there was beginning reaction, such as vascular proliferation. There was also a mild diffuse "toxic" process, characterized by chromatolysis and pyknosis of nerve cells and slight microglial and macroglial proliferation. The above lesions suggested a condition resembling periarteritis nodosa, which had apparently affected the brain only mildly with the exception of the terminal stage of the illness. The concurrence of chronic and acute subintimal angiitis and the predilection for the small blood vessels were in keeping with a diagnosis of periarteritis nodosa. Whatever underlying malformation of the brain was present was difficult to evaluate because it was obscured by the acute changes.

Diagnosis: (1) Acute encephalopathy secondary to periarteritis nodosa. (2) Possible cerebral malformation.

Discussion

The immediate cause of death was not fully recognized until the results of the histologic examination of the brain became known. Severe kidney damage was obvious from the first day of the patient's last illness. The pulmonary edema and bronchopneumonia were considered as terminal. The persistent headache, convulsions, emesis and progressive state of drowsiness were considered as due to uremia, although the azotemia was not very high. When convulsions took place the possibility of brain involvement in the arterial disease was thought of, but it was dismissed because of the infrequency of angiitis of the central nervous system.[1, 4g, 14, 17, 19] In retrospect, it is obvious that it was the increased intracranial pressure that was responsible for the terminal events. It is also possible that the cortisone therapy aggravated the condition by increasing the cerebral edema,[2, 19] although the cortisone was discontinued as soon as the first indication of edema appeared, three days before the convulsions began. There were only two convulsive seizures, nine days before death. The generalized edema was in evidence only the last few days, 10 to 12 days after the last dose of cortisone. Nevertheless, it is likely that the cortisone, acting as a trigger mechanism, upset the hormonal balance and indirectly led to the terminal events.

Differential Diagnosis: Sarcoidosis was considered but was excluded because of the x-ray appearance of the lungs and of the small bones of the extremities, the leukocytosis (instead of leukopenia), the normal A:G ratio, and the absence of peripheral lymphadenopathy and of skin lesions. Pulmonary tuberculosis was under strong suspicion for over two years, but was excluded on clinical grounds: negative skin tests, negative guinea pig inoculations, and the marked discrepancy between the x-ray appearance of the lungs and the well-being of the patient.[12, 22] Coccidioidomycosis and histoplasmosis were excluded by skin tests. Postmortem findings did not disclose any evidence of the above diseases. The diagnosis of periarteritis nodosa (old terminology) seems clinically well founded and adequately substantiated by the autopsy. There is nothing to account for the glomerulonephritis etiologically (and it developed in a comparatively short period) other than the rapidly progressive arteriolar disease.[3, 4, 5, 13] The development at the same time of granulomatous lesions in the liver, spleen, lungs and lymphatic system makes the diagnosis more definite.[12, 17, 21, 23]

In a recent report Bertram [3] emphasizes that "one must consider periarteritis nodosa whenever there is hematuria in a relatively young patient." Boyd,[4] in a

very extensive review of the subject, points out that "the occurrence of rapidly increasing hypertension in the course of a subacute febrile syndrome is peculiar and suggests periarteritis nodosa." Many writers on the subject stress the point that whenever several systems are involved periarteritis is to be thought of. This patient had always shown evidence of allergic sensitivity. The relationship of allergy and periarteritis in many cases has been definitely demonstrated.[5, 6, 8, 10, 11] There had been in this case marked and long-standing pulmonary involvement proved as far as was possible to be nontuberculous, and not typical of any common form of pulmonary disease. In addition rapidly progressing failure of kidney function, and unexplained hepatomegaly and splenomegaly both pointed to the diagnosis of periarteritis nodosa.

As was mentioned in the opening paragraph, the symptomatology of the cases reported has varied in a wide range. Viewed in the light of recent contributions on the subject, particularly those of Zeek and her collaborators, periarteritis is only one of several types of arterial diseases, to all of which she gives the generic name of necrotizing angiitis. Many entirely unrelated syndromes can develop on the basis of an underlying necrotizing arteriolar disease.

Cortisone Therapy: There are a number of reports of good results obtained by the administration of cortisone.[7, 16, 19] In this case a drop in temperature, lowering of blood pressure and diminution of size of the liver and spleen were noted. The secondary effects (moon-face, periorbital edema) compelled the withdrawal of the drug. To what extent, if at all, the cortisone was responsible for the rapid progress of the cerebral complication, or was the immediate cause of death, it is hardly possible to tell. It has been said that hormone therapy is ineffectual in cases with advanced kidney disease, and that it must be given early in the disease if curative results are to be hoped for. Temporary remissions, however, are reported in many cases. Though the prognosis in cases with advanced renal lesions is bad, if not hopeless, one is not justified in withholding hormonal therapy even when good results can hardly be expected. It is interesting to note that even in unsuccessful cases (the patient dying of the disease), the small arteries on histologic examination are found to be in a healed state, showing fibrous obliteration of the lumina of the vessels.[2] The cure thus would seem to be worse than the disease, but nevertheless the favorable reports of the use of hormone therapy far outweigh the unfavorable ones.

Summary

A case is presented of necrotizing angiitis with postmortem histologic findings in the brain. The differential diagnosis and the basis for the diagnosis in this case are given. Cortisone therapy is discussed briefly.

BIBLIOGRAPHY

1. Arkin, A.: A clinical and pathological study of periarteritis nodosa, Arch. Int. Med. **58**: 993 (Dec.) 1936.
2. Baggenstoss, A. H., Shick, R. M., and Polley, H. I.: The effect of cortisone on the lesions of periarteritis nodosa, Am. J. Path. **27**: 537 (July-Aug.) 1951.
3. Bertram, W.: Diagnose und Therapie der Periarteritis nodosa, München. med. Wchnschr. **94**: 1205 (June 13) 1952.

4. (a) Boyd, L. J.: The clinical aspects of periarteritis nodosa, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 1: 219 (Dec.) 1938.
(b) Boyd, L. J.: The clinical aspects of periarteritis nodosa, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 3: 32 (Apr.) 1940.
(c) Boyd, L. J.: Periarteritis nodosa, cutaneous symptoms, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 3: 173 (Oct.) 1940.
(d) Boyd, L. J.: Periarteritis nodosa, neuromyositic manifestations, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 3: 272 (Dec.) 1940.
(e) Boyd, L. J.: Periarteritis nodosa, abdominal manifestations, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 4: 27 (Apr.) 1941.
(f) Boyd, L. J.: The renal and cardiac manifestations of periarteritis nodosa, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 4: 176 (Dec.) 1941.
(g) Boyd, L. J.: The cerebral and ocular manifestations of periarteritis nodosa, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 6: 130 (Oct.) 1943.
(h) Boyd, L. J.: Pulmonary manifestations of periarteritis nodosa, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 7: 94 (Oct.-Dec.) 1944.
5. (a) Case Record of the Mass. Gen. Hosp. No. 25144, New England J. Med. 220: 600 (Apr. 6) 1939.
(b) Case Record of the Mass. Gen. Hosp. No. 39142, New England J. Med. 248: 609 (Apr. 2) 1953.
(c) Case Record of the Mass. Gen. Hosp. No. 31241, New England J. Med. 232: 704 (June 14) 1945.
6. Churg, J., and Strauss, L.: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa, Am. J. Path. 27: 277 (Mar.-Apr.) 1951.
7. Doenhardt, A., and Mies, J. H.: Beitrag zur Fruehzeitigen Diagnose der Periarteritis nodosa, Klin. Wchnschr. 30: 492 (June 1) 1952.
8. Harkavy, J.: Vascular allergy, J. Allergy 14: 507 (Nov.) 1943.
9. Harris, A. W., Lynch, G. W., and O'Hare, J. P.: Periarteritis nodosa, Arch. Int. Med. 63: 1163 (June) 1939.
10. Jackson, A., and Kass, I.: The relationship between periarteritis nodosa and sarcoidosis, Ann. Int. Med. 38: 288 (Feb.) 1953.
11. Klemperer, P.: Diseases of the collagen system, Bull. New York Acad. Med. 23: 581, 1947.
12. Lindsay, S., Aggeler, P. M., and Lucia, S. P.: Chronic granuloma associated with periarteritis nodosa, Am. J. Path. 20: 1057 (Nov.) 1944.
13. Lohse, R.: Zur klinischen Diagnose der Periarteritis nodosa, Deutsche med. Wchnschr. 77: 47 (Jan. 11) 1952.
14. Malamud, N., and Foster, D. B.: Periarteritis nodosa: a clinico-pathological report with specific reference to the central nervous system, Arch. Neurol. and Psychiat. 47: 828 (May) 1942.
15. McGurl, T. J.: Periarteritis nodosa: report of a case treated with para-aminobenzoic acid, Ann. Int. Med. 37: 606 (Sept.) 1952.
16. Mundy, W. L., Walker, W. G., Bickerman, H. A., and Beck, G. J.: Periarteritis nodosa: report of a case treated with ACTH and cortisone, Am. J. Med. 11: 630 (Nov.) 1951.
17. Newman, W., and Wolf, A.: Non-infectious granulomatous angiitis involving the central nervous system, Tr. Am. Neurol. A. 77: 114–117, 1952.
18. (a) Schottstaedt, W. E. R.: Periarteritis nodosa with remission of symptoms, California and West. Med. 36: 186 (Mar.) 1932.
(b) Schottstaedt, W. E. R.: Personal communication.
19. Shick, R. M., Baggenstoss, A. H., and Polley, H. F.: Effect of cortisone and ACTH on periarteritis nodosa and cranial arteritis, Proc. Staff Meet., Mayo Clin. 25: 135 (Mar. 15) 1950.

20. Spiegel, R.: Clinical aspects of periarteritis nodosa, Arch. Int. Med. **58**: 993 (Dec.) 1936.
21. Sweeney, A. R., and Baggenstoss, A. H.: Pulmonary lesions in periarteritis nodosa, Proc. Staff Meet., Mayo Clin. **24**: 35 (Jan. 19) 1949.
22. Symmers, W. St. C., and Litchfield, J. A.: Healing polyarteritis nodosa: observations on 3 cases after ACTH and on one case after sympathectomy, Lancet **2**: 1193 (Dec. 20) 1952.
23. Weinberg, T.: Periarteritis nodosa in granuloma of unknown origin, Am. J. Clin. Path. **16**: 784 (Dec.) 1946.
24. (a) Zeek, P. M.: Periarteritis nodosa: a critical review, Am. J. Clin. Path. **22**: 777 (Aug.) 1952.
(b) Zeek, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis, New England J. Med. **248**: 764 (Apr. 30) 1953.
(c) Zeek, P. M., Smith, C. C., and Weeter, J. C.: Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and hypersensitivity, Am. J. Path. **24**: 889, 1948.

EDITORIAL

ON THE PRODUCTION OF HALLUCINATED AND PSYCHOSIS-LIKE STATES

One way of studying a condition is to produce it experimentally. Since so many different factors go into as complex a piece of human behavior as hallucinations, we will discuss two different approaches to the experimental production of hallucinated and psychosis-like states. One group of methods is concerned with the chemistry of the body. Another group involves the environment of the subject. Other approaches such as electrical stimulation of the cortex could be discussed. We made our choices because we wish to suggest a possible relationship between these two particular approaches.

One is occasionally asked if a particular patient's hallucinations are organically or psychologically determined. The misleading aspects of such an either/or question in this field are demonstrated by several recent studies. Lasagna et al.[1] have found personality differences to distinguish subjects who are depressed by amphetamine from the more common subjects who find it an euphoriant. Kornetsky[2] has been able to predict, on the basis of psychological testing, those members of a group of addicts who will become hallucinated on acute barbiturate withdrawal. Certainly the reaction of a given subject is a function both of his thoughts and his chemistry, with thoughts influencing chemistry and vice versa. Since we will discuss a chemical method of inducing hallucinations first, the influence of chemistry on thought will receive ample emphasis. However, these transactions are two-way affairs. We are familiar with the fact that thoughts can evoke emotions and that emotions can cause autonomic and endocrine changes. Over and above this, it is generally conceded that mental activity must have its physico-chemical correlates, and differing mental states must have physico-chemical correlates which differ at least in pattern. Having duly emphasized the complexity of our subject, let us turn our attention to pharmacological methods of inducing hallucinations.

Pharmacological Methods of Inducing Hallucinations

Man has, from antiquity, been interested in methods of making himself ill. Hallucinations and delirious states can be induced by a variety of toxic substances, and one of the attractions of drugs like cannabis and mescaline depends in part on the bizarre mental states they produce. Cannabis is also known as marihuana and as hashish. Mescaline is the active ingredient of the cactus bud used in religious ceremonies by American Indians.

The history of psychiatric interest in such hallucinogenic drugs (known also as phantastica, psychotica, or hallucinogens) has been reviewed by Mayer-Gross.[3] He credits Moreau de Tours with opening this field in

[1] Lasagna, L., et al.: Drug-induced mood changes in man, J.A.M.A. In press.

[2] Kornetsky, C.: Relationship between Rorschach determinants and psychosis in barbiturate withdrawal syndrome, A.M.A. Arch. Neurol. and Psychiat. 72: 452, 1954.

[3] Mayer-Gross, W.: Experimental psychoses and other mental abnormalities produced by drugs, Brit. M. J. 2: 317, 1951.

1845. Regardless of one's preferred approach to mental disease, such studies have potential value. It is quite conceivable that various psychological states which are associated with altered relationships to reality may also be similar in some physiologic sense. It is conceivable that they might even have some toxic metabolite in common. Leaving aside considerations as to whether such a theoretical toxic substance would be exogenous, due to congenital metabolic abnormality, the product of a disease of adaptation, or some result of a physiological response to stress, the identification of such a substance would be of considerable value.

DeJong's work [4] represents one recent attack on this problem. In animal experiments, he found that only alterations in the functions of the liver and intestines were capable of producing signs of experimental catatonia (p. 224). Other workers had reported altered liver function tests in schizophrenia. DeJong found that bulbocapnine produced strikingly catatonic-like behavior in animals. Since a bulbocapnine-like compound might be produced in hepatic disease, he attempted to implicate such a compound in clinical catatonia.

One of the objections to this work concerns the fact that bulbocapnine must be given in relatively large doses to be effective. Many other substances will produce similar changes if given in large enough dosages. Body chemistry in most clinical psychoses is not grossly different from normal. The presence of gross amounts of some abnormal metabolite in clinical psychoses seems unlikely, and it would be much more convincing if the hypothetical toxic substance were hallucinogenic in minute quantities. A substance meeting this criterion is lysergic acid diethylamide, known also as LSD-25. This ergot derivative was first prepared around 1937 and has been receiving considerable attention as an hallucinogen in the recent literature.[5-15] In doses on the order of 100 micrograms it produces turmoil

[4] deJong, H. H.: Experimental catatonia, 1945, The Williams & Wilkins Co., Baltimore.
[5] Stoll, A., and Hoffmann, A.: Partial synthesis of alkaloids of the type of the ergobasin, Helv. chim. Acta **26**: 944, 1943.
[6] Stoll, W. A.: Lysergic acid diethylamide. A fantasticum of the ergot group, Schweiz. Arch. f. Neurol. u. Psychiat. **60**: 279, 1947.
[7] Hoch, P. H., et al.: Effects of mescaline and lysergic acid diethylamide (LSD-25), Am. J. Psychiat. **108**: 579, 1952.
[8] Savage, C.: Lysergic acid diethylamide (LSD-25). A clinical-psychological study, Am. J. Psychiat. **108**: 896, 1952.
[9] Sloane, B., and Doust, J. W. L.: Psychophysiological investigations in experimental psychoses: Results of the exhibition of D-lysergic acid diethylamide to psychiatric patients, J. Ment. Sc. **100**: 129, 1954.
[10] Pennes, H. H.: Clinical reactions of schizophrenics to sodium amytal, pervitin hydrochloride, mescaline sulfate, and D-lysergic acid diethylamide (LSD-25), J. Nerv. and Ment. Dis. **119**: 95, 1954.
[11] Forrer, G. R., and Goldner, R. D.: Experimental physiological studies with lysergic acid diethylamide (LSD-25), Arch. Neurol. and Psychiat. **65**: 58, 1951.
[12] Abramson, H., et al.: Lysergic acid diethylamide (LSD-25): I. Physiological and perceptual responses, J. Psychol. **39**: 3, 1955.
[13] Rinkel, M., Hyde, R. W., and Solomon, H. C.: Experimental psychiatry. III. A chemical concept of psychosis, Dis. Nerv. System **15**: 259, 1954.
[14] Fischer, R.: Factors involved in drug-produced model psychoses, J. Ment. Sc. **100**: 623, 1954.
[15] DeShon, H. T., et al.: Mental changes experimentally produced by LSD, Psychiat. Quart. **26**: 33, 1952.

states and hallucinations in "normal" humans and augments the symptomatology of schizophrenic patients.

We have noted that the personality of a subject will influence the form of his reaction to any drug. In this light we would not expect the reaction of normals under the influence of a drug to mimic exactly any particular clinical psychosis. In actual fact, drug-treated experimental subjects usually retain insight and recognize that their experiences are temporary and drug-induced. One may also pick out differences between lysergic acid-induced hallucinations and clinical hallucinations. Under lysergic acid, some subjects describe visual impressions produced by sound and auditory impressions produced by light. This "seeing noise" and "hearing vision" is known as synesthesia and is practically unheard of in clinical practice. In spite of these differences, it is still reasonable to hope that lysergic acid may bear a relationship to one factor operating in some clinically occurring hallucinated states. Excellent English descriptions of lysergic acid-induced psychosis are available in the works of Hoch et al.,[7] Savage,[8] Sloane and Doust,[9] Pennes,[10] Forrer and Goldner,[11] Abramson et al.,[12] and DeShon et al.[15] Here, however, we are concerned with what light this drug may throw on the development of clinical hallucinations, and so our question is: How does this substance act?

It would be ideal if we could state just how lysergic acid affects brain metabolism. At present, however, many older ideas about cerebral metabolism are being changed. For instance, glucose was once considered the sole metabolite of the brain. Work by Grenell and Davies[16] and by Geiger et al.[17] indicates that this is not the case. Such a condition makes a complete general theory unlikely in the near future. There are, however, a variety of interesting (and on some occasions unnecessarily independent) observations on lysergic acid which all seem in one way or another to implicate the sympathetic branch of the autonomic nervous system.

In an interesting speculative paper, Rinkel, Hyde and Solomon[13] have marshalled a diverse group of arguments to support the contention that lysergic acid interferes with adrenalin synthesis. They have noticed that obvious autonomic phenomena accompany the administration of lysergic acid. Subjects may show changes in pulse rate, blood pressure, pupil size, sweating, and other functions. They cite the work of Funkenstein[18] who has related norepinephrine and epinephrine to extra- and intra-punitive anger, respectively. Funkenstein's theories are related to observations made on changes in blood pressure response of subjects to injected mecholyl. They also cite the work of Witt[19] who noted that lysergic acid-treated

[16] Grenell, R. G., and Davies, P. W.: Respiration of the cerebral cortex in vivo in the absence of glucose, Fed. Proc. Am. Soc. Exper. Biol. 9: 52, 1950.

[17] Geiger, A., Magnes, J., and Geiger, R. S.: Survival of the perfused cat's brain in the absence of glucose, Nature 170: 754, 1952.

[18] Funkenstein, D. H., et al.: The direction of anger during a laboratory stress-inducing situation, Psychosom. Med. 16: 404, 1954.

[19] Witt, P. N.: D-lysergic acid diethylamide in the spider test, Experientia 7: 310, 1951.

spiders spin finer strands into more regular webs. They state that the spider's web is composed largely of adrenalin and feel that the finer strands indicate a block in adrenalin synthesis. They note certain of the metabolic diseases, such as phenylpyruvic oligophrenia and albinism, which are related to a disturbance in the phenyl-alanine-tyrocine-adrenalin cycle are also frequently associated with mental symptoms. Finally, Rinkel and his co-workers note the work of Hoffer, Osmond and Smythies.[20] This latter group has speculated on the relationship between hallucinogens and the sympathetic nervous system by noting the similarity between mescaline and adrenalin. These workers felt that they could produce psychotic symptoms by administering adrenochrome, a possible sympathetic amine metabolite. Rinkel and his co-workers were unable to repeat this but feel that Hoffer and his co-workers used an adrenochrome solution containing adrenoxane as a contaminant, and that the adrenoxane was the hallucinogenic agent. In this way they still maintained the relationship between hallucinogenic activity and the effect on the sympathetic nervous system. Other evidence is presented by Rinkel et al., but some of it is ambiguously stated. We hope that future publications from this group will clarify such remarks as the following sentence from p. 261: "There was only a slight reaction of the parasympathetic nervous system to 2.5 mgm. of Mecholyl after the effect of LSD had become manifest."

Fischer[14] arrived at his implication of the sympathetic nervous system by an entirely different route. He gives three lines of evidence to support the notion that fibrous wool protein may serve as a model of the structural surface of receptors possibly involved in drug-induced psychosis. He then uses the "sorption" of compounds onto wool protein as a model of the action of these drugs on certain central nervous system structures. He studied mescaline, methamphetamine (methedrine) and lysergic acid, and found that there was an inverse relationship between the affinity of these drugs for wool protein and the logarithm of the dosage required to produce a model psychosis. He notes certain chemical similarities and concludes that " . . . sympathetic overtonus and subsequent adrenergic blockade are apparently among the factors contributing to the precipitation of a model psychosis." In support of this conclusion, he notes that anxiety has a potentiating effect on the hallucinogenic properties of lysergic acid.

Methedrine is known to augment symptoms in clinical schizophrenia[10, 21] and the relationships between this drug and lysergic acid are interesting. Methedrine and lysergic acid both are capable of causing an increase in blood adrenalin.[22] Luminal, on the other hand, depresses it.[23] Amytal is

[20] Hoffer, A., Osmond, H., and Smythies, J.: Schizophrenia: A new approach. II. Result of a year's research, J. Ment. Sc. **100**: 29, 1954.

[21] Hope, J. M., et al.: Intravenous pervitin in the psychopathology of schizophrenia, Dis. Nerv. System **12**: 3, 1951.

[22] Liddell, D. W., and Weil-Malherbe, H.: The effects of methedrine and of lysergic acid diethylamide on the mental processes and on the blood adrenalin level, J. Neurol., Neurosurg. and Psychiat. **16**: 7, 1953.

[23] Kinzius, H.: Changes in the epinephrine content of blood following amphetamine, phenobarbital, and alcohol, Arbeitsphysiol. **14**: 243, 1950.

reported to reduce temporarily the symptoms in schizophrenia.[10, 24] Elkes et al.[25] noted that lysergic acid and amphetamine both produce electroencephalographic and behavioral alerting in animals. This alerting is that state which frequently follows some noxious stimulus, is intimately related to sympathetic nervous discharge and which is counteracted by barbiturates. Theoretically, this electroencephalographic alerted state is dependent upon the ascending reticular system.

It is apparent from this brief review that no really satisfying theory has been presented. One can summarize these apparent facts, however. Lysergic acid and most other hallucinogens exert an effect on autonomic activity. There are chemical similarities, albeit sometimes remote, between hallucinogens and the sympathetic amines. Methedrine and lysergic acid have an action on the electrical activity of the brain which is similar to that alerting which follows a noxious stimulus and which accompanies sympathetic discharge. Emotionally disturbing situations may cause an exacerbation of clinical psychotic reactions and may facilitate the psychosis-producing effects of lysergic acid. With due caution, we may theorize that there is some relationship between hallucinogenic activity and autonomic activity, but we dare to go no further. Let us then turn our attention to the possibilities of producing hallucinations by manipulating the external rather than the internal environment of the subject.

Psychological Methods of Inducing Hallucinations

He have already emphasized the importance of mental states on drug reactions. Psychological methods may also be used to produce hallucinations without the help of drugs. Hypnosis is one obvious possibility. The technic of hypnosis consists of limiting the sensory environment of the subject to some type of contact with the hypnotist. The subject may lie on a couch in a darkened room with his eyes closed and listen to the voice of the hypnotist. Hallucinations are induced by the hypnotist who supplies what is essentially a false sensory environment. In other words, the hypnotist suggests the hallucination.

Bexton et al.[26] have reported that hallucinations may be produced without any suggestions being given to the subject, simply by reducing the variations in the subject's sensory environment. They used a variety of devices to limit as much as possible any sensory stimuli that the subject might encounter. They found that in a very short time the mental functioning of

[24] Gottlieb, J. S., et al.: Psychopharmacologic study of schizophrenia and depressions. II. Comparison of tolerance to sodium amytal and amphetamine sulfate, Arch. Neurol. and Psychiat. **54**: 372, 1945.

[25] Elkes, J., Elkes, C., and Bradley, P. B.: The effect of some drugs on the electrical activity of the brain, and on behavior, J. Ment. Sc. **100**: 125, 1954.

[26] Bexton, W. H., et al.: Effects of decreased variation in the sensory environment, Canad. J. Psychol. **8**: 70, 1954.

the subject began to deteriorate and that hallucinations finally made their appearance. From their observations, it would seem that the validity of our thoughts must constantly be checked against the outside world, for if they are left to develop on their own psychosis results. The human mind, freed from the mundane demands of reality, becomes unrealistic, sick and unreliable.

Hebb presented data at the Laurentian Conference on the hallucinogenic effect of reduced sensory variations. Brazier,[27] in reviewing this, noticed how Hebb's data contrasted with the experiences recorded by Courtauld in his diary. Courtauld was, according to Dr. Brazier, buried in a snow hut for some time with no light, but apparently he developed no psychosis. It would seem, however, that the absence of light does not define a restricted sensory environment, and Courtauld, struggling for survival in his snow hut, may have had a rich enough variety of sensory experiences to make up for his lack of retinal stimulation. For example, the writings of Helen Keller attest to the richness of her experience in spite of the limitations in sensory channels available to her.

A Suggested Relationship Between the Two Methods

The observations that we have presented are interesting, perhaps suggestive, but certainly far from definitive. There seems little relationship on the surface between observations on lysergic acid and observations of the effects of reduced sensory stimulation. It is possible, however, to suggest a way in which these two sets of observations may possibly be related. Observations of our own and others[28] suggested that procedures which may evoke sympathetic activity may also create a more limited sensory environment. We observed that subjects tended to make less of a muscular startle response to sudden loud sounds when their pulse rates had been raised by inhaling amyl nitrite than they did under control conditions.[29] A similar effect was produced by methamphetamine, although we had expected this stimulant to make our subjects show more of a startle response.

This effect of methamphetamine should perhaps have been predicted. Laufer and Denhoff,[30] in discussing the well-known beneficial effect of amphetamine on the hyperkinetic syndrome of behavior in children, state: "It is our conception that underlying the hyperkinetic syndrome is a dysfunction of the diencephalon which could make the individual unusually sensitive to stimuli flooding in from both peripheral receptors and viscera." This

[27] Brazier, M. A. B.: Symposium report. The Laurentian Symposium on the electrical activity of the cortex as affected by the brain stem reticular system in relation to states of consciousness, Electroencephalog. and Clin. Neurophysiol. 6: 355, 1954.

[28] Callaway, E., and Thompson, S. V.: Sympathetic activity and perception, Psychosom. Med. 15: 443, 1953.

[29] Callaway, E., and Dembo, D.: Sympathetic activity and perception. II. Paper read at 1954 annual meeting of the American Psychiatric Association.

[30] Laufer, M. W., and Denhoff, E.: Possible relationship of a type of children's behavior disorder and dysfunction of the diencephalon. Paper read at International Institute on Child Psychiatry, Toronto, 1954.

notion of a diencephalic-autonomic dysfunction is supported by Lourie's finding of excessive salivation in such patients.[31] On the neurophysiological side, Marrazzi[32] has accumulated much evidence to indicate that some of the sympathetic and sympatho-mimetic amines inhibit synaptic transmission.

Kinsey et al.,[33] in describing the physiology of orgasm, list a variety of autonomically controlled effects including hypertension, increased pulse rate, and sweating. They also devote a section to discussing the striking diminution in sensory perception found during orgasm (p. 613). Is this an example of limiting of sensory perception being co-existent with an alerted state? It is a relatively common observation that an athlete in the height of excitement may suffer serious injury without being aware of it.

One may also invoke the classic Yerkes-Dodson theory.[34] It states that there is an optimum level of stress or alerting for any task which is inversely related to the difficulty of the task. In terms of the Yerkes-Dodson theory, the more complex task would require a broader panorama of the environment. The additional sensory data needed to cope with the complex task would be more readily available at lower tension levels. The simple task would require a direct reaction to a simple stimulus and would not be interfered with by a limited sensory environment.

A possible neurophysiological mechanism by which alerting might limit sensory inflow is suggested by the cat experiments of Hagbarth and Kerr.[35] They observed that stimulating the ascending reticular substance diminishes spinal afferent conduction.

If our theory has any validity, it might indicate this about some psychotic reactions: The more stress some people are subjected to, the less environmental stimuli they are free to use; the less of the environment they are free to draw upon, the poorer their judgment becomes; the poorer their judgment becomes, the less they are able to avoid stress; and the more stress they are subjected to, the less of the environment they are able to use for future judgments. Thus a vicious cycle of psychosis may establish itself.

Conclusion

The observations which have been chosen for the above discussion have been those most easily fitted into our particular theoretical framework. We have been preoccupied with the possible interrelationship or transaction between autonomic activity, sensory deprivation, and distorted perception.

[31] Lourie, R. S.: Rate of secretion of parotid glands in normal children, A. M. A. J. Dis. Child. **65**: 455, 1943.

[32] Marrazzi, A. S., et al.: Pharmacology of the nervous system, Progress in Neurol. and Psychiat. **9**: 75, 1954.

[33] Kinsey, A. C., et al.: Sexual behavior in the human female, 1953, W. B. Saunders & Co., Philadelphia.

[34] Yerkes, R. M., and Dodson, J. D.: The relation of strength of stimulus to rapidity of habit-formation, J. Comp. Neurol. **18**: 459, 1908.

[35] Hagbarth, K. E., and Kerr, D. I. B.: Central influences on spinal afferent conduction, J. Neurophysiol. **17**: 295, 1954.

There is, as we hinted, another universe of observations that would find this viewpoint a Procrustean bed.

The subject of serotonin (5-hydroxytryptamine) has been reviewed by Page[36] who believes this interesting, naturally-occurring compound plays an active role in vascular homeostasis and in nerve metabolism. Lysergic acid is extremely active as a serotonin antagonist and Page quotes Gaddum as stating: " . . . it is possible that the H-T (serotonin) in our brains plays an essential part in keeping us sane and the effect of LSD is due to its inhibitory action on the H-T in the brain." Similar views have been given by Woolley and Shaw.[37] Although the function of serotonin may be intimately related to the autonomic nervous system, no unstrained integration of these findings into our theory suggests itself. Mayer-Gross[38] has suggested that lysergic acid may act by affecting carbohydrate metabolism. This approach is even more remote from our theoretical framework.

There are also psychological observations which are not readily handled by our theory. Hypnogogic hallucinations occur when one is fatigued and drowsy. An EEG taken at such a time would show quite the opposite from so-called electroencephalographic alerting. Sympathetic activity is at a low ebb at such a time, yet hallucinations may occur. We have noted the almost anesthetic effect of extreme alerting and stress, but Kornetsky[39] has shown that morphine raises the threshold for pain only in anxious subjects. Presumably, morphine acts by reducing the anxiety, but anxiety is related to this alerted adrenergic state. Here we find a decrease in alerting related to a decrease in pain threshold.

Faced with this state of affairs, we must recognize the multiple interreactions that go into so complex a thing as human hallucinations. We should be naive indeed to hope for a single factor of universal etiologic significance. An increasing number of specific transactions of useful but limited generality will be found. One might predict, however, that for some time to come the physician who concerns himself with more complex aspects of human behavior will be faced with considering the so-called total person. He will have to evaluate social, physiological, chemical, genetic, cultural, educational, and psychological factors for each individual patient and select the most vulnerable areas for what he hopes will be a therapeutic assault on the problems of that unique sick human.

ENOCH CALLAWAY III

[36] Page, I. H.: Serotonin (5-hydroxytryptamine), Physiol. Rev. **34**: 563, 1954.
[37] Woolley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin, Brit. Med. J. **2**: 122, 1954.
[38] Mayer-Gross, W., et al.: Psychological and biochemical effects of lysergic acid diethylamide, Nature **168**: 827, 1951.
[39] Kornetsky, C.: Effects of anxiety and morphine on the anticipation and perception of painful radiant thermal stimuli, J. Comp. Physiol. and Psychiat. **47**: 130, 1954.

REVIEWS

The Pathology of Trauma. 2nd Ed. By ALAN RICHARDS MORITZ, M.D., Professor of Pathology and Director of the Institute of Pathology of the School of Medicine of Western Reserve University, Cleveland. 414 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1954. Price, $8.50.

As civilization has become more mechanized, there has been a parallel increase in mortality and morbidity from bodily injuries. However, the anatomical, physiological and psychological alterations resulting from trauma are almost completely ignored by present medical school curricula. Consequently *The Pathology of Trauma* is a book that fills the need for such enlightenment. The second edition, a thorough revision, presents in an excellent, easily readable manner the anatomical, physiological and psychiatric aspects of trauma.

A chapter devoted to injuries of each of the cardiovascular, respiratory, gastrointestinal, biliary, genito-urinary, central nervous, and musculoskeletal systems makes for easy reference. Additional chapters devoted to the general effects of mechanical injuries such as gunshot wounds, explosive injuries, the relation of trauma to infection and tumors are authoritatively and interestingly presented so that the basic pathologic changes cannot be misinterpreted.

There is detailed information regarding the medicolegal autopsy which has not previously been so conveniently recorded. The chapter covering head injuries is the best treatment of this subject published.

The original edition has been expanded and presented in greater detail with more numerous illustrations and an up-to-date bibliography. An understanding of the information contained in this volume is paramount for clinicians, coroners, industrial physicians, surgeons, medical examiners, pathologists and physicians in all fields of medicine because of the increasing importance of mechanical injury.

WILLIAM V. LOVITT, JR.

Lehrbuch der Krankheiten des Herzens und der Blutstrombahn. By Prof. Dr. FRITZ LANGE. 631 pages; 16.5 × 24.5 cm. Ferdinand Enke Verlag, Stuttgart. 1953. Price, Geheftet DM 67.—; Ganzleinen DM 71.—.

The writing of a concise text of the diseases of the heart and peripheral arteries is a difficult task. The author is fully aware, to judge from the preface of his book, that the blending of the newly gained knowledge of circulatory pathophysiology and clinical diagnosis and management has to be achieved to prove it useful. The text is addressed to the physician as well as the student. While the physician requires clinically useful information sufficiently explained by means of our present day understanding of things, the student should be exposed to concepts and pathophysiology to a greater extent to facilitate his development in biological and clinical thinking.

The reviewer has his doubts that both parties can be served equally well within a feasible book size. The author's attempts are worthy of praise. Many chapters are interesting, particularly those on hemodynamics and function tests. Knowledge newly gained through cardiac surgery is hardly incorporated as are many others obtained through cardiac catheterization, etc. Myocardosis is a concept of little interest and pneumopericardium does not deserve an entire page for its presentation.

The book itself contains too little information for the physician and is not sufficiently coordinated to be of value to the medical student. The presentation is clear and well illustrated. The printing and reproductions are excellent. There are many English texts on cardiology available which are superior to the one reviewed here.

A. G.

Handbook for Diabetic Children. By ALFRED E. FISCHER, M.D., Associate Attending Pediatrician and Chief of the Children's Diabetic Clinic, Mount Sinai Hospital, New York City; and DOROTHEA L. HORSTMAN, Instructor in Dietetics, School of Nursing, Mount Sinai Hospital, New York City. 64 pages; 14 × 21.5 cm. (paper-bound). Intercontinental Medical Book Corporation, New York. 1954. Price, $1.75.

The authors wrote this revised edition to fill the need for a simple handbook which can be easily understood by a child or his parents. Two-thirds of the book are devoted to foodstuffs, meal planning, dietary exchanges, sample menus and hints for variety and tastiness in cooking. The remainder contains instructions on how to use insulin, the technic of insulin injections, exercising, how to keep healthy, and how to keep records for the doctor.

Medical students will profit from the clear exposition. Practicing physicians, themselves, may not feel that this book is too juvenile for their own perusal. It is unlikely therefore that physicians will put this into the hands of their young patients, or of their bewildered, guilt-laden parents without concurrent repeated sessions of teaching. Used as an instructor's notes it is admirable; used as the instructor's replacement, the anxiety it might cause surely would defeat the aim of the writers.

P. F.

Roentgen-Diagnostics (Volume IV, Gastrointestinal Tract, Gynecology, Urology). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, and E. UEHLINGER. First American Edition (based on the Fifth German Edition), English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 946 pages (pages 3099–4029); 19.5 × 28 cm. Grune and Stratton, New York. 1954. Price, $50.00.

Roentgen-Diagnostics is the English edition of the *Lehrbuch der Roentgen Diagnostik,* which for many years has been an outstanding radiologic reference. Volume IV of this great treatise superbly covers the gastrointestinal and genitourinary tracts.

As in the first three volumes, fundamentals of normal anatomy and its alterations by disease are stressed. While the pathological and clinical manifestations of all diseases of these two important systems are adequately discussed, emphasis is on the roentgen manifestations, which are profusely and magnificently illustrated with high quality roentgenograms, sketches and an occasional chart.

Not only this volume, but the entire set of *Roentgen-Diagnostics* is the most complete radiologic reference published in English. Through its exposition of fundamentals and its vast clinical contents, *Roentgen-Diagnostics* will be an extremely useful reference in all medical specialties which are highly dependent upon diagnostic roentgenography.

J. M. D.

Roentgen-Diagnostics (Cumulative Index). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, and E. UEHLINGER. First American Edition (based on the Fifth German Edition), English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 103 pages; 19 × 28 cm. Grune and Stratton, New York. 1954. Price, $10.00.

The Cumulative Index of *Roentgen-Diagnostics* is quite complete and undoubtedly useful. However, the price of this book is out of proportion to its useful-

ness since each of the four volumes has its Table of Contents and Index, which are complete and well organized and will serve the same purpose.

J. M. D.

Emergency Treatment and Management. By THOMAS FLINT, JR., M.D., Director, Division of Industrial Relations, Permanente Medical Group, Oakland and Richmond, California; Chief, Emergency Department Permanente Medical Group, Kaiser Foundation Hospital, Richmond, California. 303 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1954. Price, $5.75.

The objective of this book is to outline the treatment and management of the emergency patient from the time of the first examination until the disposition of the patient for definitive therapy. The text is divided into three major sections: General Medical Principles and Procedures, Emergency Treatment of Specific Conditions and Administrative, Clerical and Medicolegal Procedures. Under these major headings the specific problems are arranged alphabetically. The largest section concerning specific medical conditions begins with a rather complete listing of the causes of "Abdominal Pain" and ends with a seven page discussion of "Wartime Emergencies."

This text is quite valuable for use in the emergency room and in the physician's office. The rapidity with which the material can be located is facilitated by the alphabetical arrangement of the text and the inclusion of an excellent index. Each procedure described is an accepted one and the author has avoided any discussion of later definitive therapy.

Some 115 pages of the book's 303 pages are devoted to specific "Poisons," "Poisonous Plants" and "Toxic Ingredients in Various Commercial Preparations." These pages gather in one place considerable information that is usually quite difficult to find. These sections on Toxicology are valuable and should allow the accident room physician to begin specific therapy with very little delay.

This text is highly recommended for the use in the hospital emergency room and for study by the younger student of medicine who will obtain knowledge of an accepted method of therapy for many of the acute ills of man.

E. R. S.

Selected Papers of Dr. Frank N. Wilson. Edited by FRANKLIN D. JOHNSTON and EUGENE LEPESCHKIN. 1090 pages; 14.5 × 22 cm. J. W. Edwards, Publisher, Inc., Ann Arbor, Michigan. 1954. Price, $10.00.

Prior to the death of Dr. Frank Norman Wilson in 1952, there were over 120 published scientific papers bearing his name. There were, in addition, many others from his laboratory to which he made notable contributions.

In this book are reprinted 53 papers which Dr. Wilson either wrote himself or which appeared from his laboratory. There are also included three previously unpublished manuscripts. The articles reproduced are included under such sections as History of Electrocardiography, Theory of Electrocardiographic Leads, Genesis of the Electrocardiogram, The Ventricular Complex in Myocardial Infarction, and others. These are reprinted in their original form and are followed by brief comments by workers associated with the original publications.

The book is well edited and the illustrations clearly reproduced. The price of the volume is particularly attractive.

With the presently increased interest in the problems of electrocardiography, this volume satisfies a real need. Many of the important papers which it contains have not been readily available in recent years. This book is also a tribute to Dr. Wilson whose work in the field of electrocardiography deserves the careful study that

a volume such as this makes possible. This book can be highly recommended to all cardiologists interested in the problems of electrocardiography, and in the contributions of Dr. Wilson and his laboratory to their solution.

L. S.

The Skin; A Clinicopathologic Treatise. By ARTHUR C. ALLEN, M.D., Associate Pathologist, Memorial Hospital. 1048 pages; 22 × 30 cm. C. V. Mosby Co., St. Louis. 1954. Price, $25.00.

The author, who is not a dermatologist, has presented a text which is intended to be all-inclusive on the clinical and pathological features of the dermatoses. In the preface he states, "in order better to effect a conjunction between dermatologists and other practitioners of medicine the edition of this book was felt justified." Throughout the text he has made an attempt to emphasize the common features, both clinically and pathologically, of lesions of the skin and mucous membrane. It is quite obvious from the histopathologic descriptions that the author has a better knowledge of the microscopic findings of skin eruptions than the average general pathologist. In conditions such as disseminated lupus erythematosus, scleroderma and metabolic diseases, he has presented the pathology of the deeper structures as well as the histopathology of cutaneous manifestations. The photomicrographs are generally excellent and the close association of the histopathological picture with the clinical picture is of great value.

Dr. Allen emphasizes that, although there has been a diminution in the number of new cases of syphilis the disease is far from the point of eradication. The description of the cutaneous lesions of syphilis is satisfactory but it is unfortunate that he has so briefly summarized the late effects of this systemic disease. He dismisses syphilotherapy with a relatively brief paragraph and advises the student to consult an authoritative treatise on the subject.

In dealing with tinea capitis, considering the severe problem imposed by this condition in recent years, the author spends too little time in clinical descriptions of the disease and almost completely neglects therapy.

Approximately one quarter of the text is devoted to neoplastic diseases, which reflects the author's extensive experience at the Memorial Cancer Center. This section of the book is excellent.

His classification of dermatoses is unorthodox but satisfactory. It is quite obvious from a perusal of this text that although his desire was to effect a better liaison between the dermatologist and other practitioners of medicine, he has more successfully attained a better understanding between the dermatologist and the pathologist.

This text will be of greatest value to the dermatologist or pathologist as a reference work. It does not replace the standard texts of dermatology already in service, but should be used more properly as a reference work.

H. M. R., JR.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Antibiotics and Antibiotic Therapy: A Clinical Manual. By ALLEN E. HUSSAR, M.D., F.A.C.P., Chief of Medical Service, Franklin Delano Roosevelt Veterans Administration Hospital, Montrose, New York; and HOWARD L. HOLLEY, M.D., F.A.C.P., Associate Professor of Medicine, Medical College of Alabama, Birmingham, Alabama, etc. 475 pages; 21.5 × 14 cm. 1954. The Macmillan Company, New York. Price, $6.00.

Behringwerkmitteilungen. Hundertjahrfeier der Geburtstage von Paul Ehrlich und Emil von Behring. 127 pages; 24 × 16 cm. (paper-bound). 1954. N. G. Elwert, Marburg/Lahn.

Diagnostik und Strahlentherapie der Geschwulstkrankheiten. By DR. MED. ALFRED VOGT. 382 pages; 26.5 × 18 cm. 1955. Georg Thieme Verlag, Stuttgart; available in the U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 72.–

Drugs in Current Use, 1955. Edited by WALTER MODELL, M.D., F.A.C.P., Associate Professor, Clinical Pharmacology, Cornell University Medical College. 147 pages; 21 × 14 cm. (paper-bound). 1955. Springer Publishing Company, Inc., New York. Price, $2.00 single copy; 4–9 copies, $1.90 each; 10 or more, $1.80 each.

Fibrosis of the Liver in West African Children. Medical Research Council Specia. Report Series No. 285. By J. H. WALTERS and J. C. WATERLOW. 98 pages. 24.5 × 15 cm. (paper-bound). 1954. Her Majesty's Stationery Office, London. Price, 8s. 6d. net.

I Cured My Cancer. By MARY PAYNE, R. T. 69 pages; 22.5 × 14 cm. 1955. Vantage Press, Inc., New York. Price, $2.50.

The Kidney: A Ciba Foundation Symposium, Arranged Jointly with the Renal Association. Editor for the Renal Association: A. A. G. LEWIS, B.Sc., M.D., M.R.C.P.; Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; assisted by JOAN ETHERINGTON. 333 pages; 21 × 14 cm. 1954. Little, Brown & Company, Boston. Price, $6.75.

Klinisch-röntgenologische Differentialdiagnostik der Lungenkrankheiten. By DR. LASAR DÜNNER. 274 pages; 28 × 19 cm. 1954. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 45.40; Gebunden DM 49.–

Love and Hate in Human Nature. By ARNOLD A. HUTSCHNECKER, M.D. 278 pages; 21 × 14 cm. 1955. Thomas Y. Crowell Company, New York. Price, $3.50.

Planning Florida's Health Leadership: Florida's Hospitals and Nurses. By JOHN M. MACLACHLAN, Ph.D. Volume IV: Medical Center Study Series, edited by LOUIS J. MALOOF. 122 pages; 23.5 × 15 cm. (paper-bound). 1954. University of Florida Press, Gainesville. Price, $1.50.

Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract. By JOHN RUSSELL TWISS, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School, etc.; and ELLIOT OPPENHEIM, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School, etc. 653 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $15.00.

Pulmonary Diseases. Edited by ROSCOE L. PULLEN, A.B., M.D., F.A.C.P., Professor of Medicine and Dean, University of Missouri School of Medicine, Columbia, Missouri, etc. 669 pages; 24 × 16 cm. 1955. Lea & Febiger, Philadelphia. Price, $15.00.

Second Congress of the International Society of Angiology, Lisbon, Portugal, September 18–20, 1953. President: Emile F. Holman, San Francisco. I. Symposium on Mitral Valvular Surgery. II. Angiology Forum. Edited by HENRY HAIMOVICI, New York, Secretary General. 433 pages; 24.5 × 16 cm. (paper-bound). 1954. Imprimerie Medicale et Scientifique (S. A.), Bruxelles. Price, $8.00.

Selected Papers of Dr. Frank N. Wilson. Edited by FRANKLIN D. JOHNSTON and EUGENE LEPESCHKIN. 1,090 pages; 22 × 14.5 cm. 1954. From the Heart Station, University Hospital, Ann Arbor, Michigan. J. W. Edwards, Publisher, Inc., Ann Arbor, Michigan. Price, $10.00.

Surgery of the Heart. By CHARLES P. BAILEY, M.D., M.Sc. (Med.), LL.D (Hon.) F.A.C.S., F.C.C.P., F.I.C.S., Professor and Head of the Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa., etc. 1,062 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $25.00.

Techniques de Réanimation Médicale et de Contrôle de L'Équilibre Humoral en Médecine D'Urgence. By J. HAMBURGER, G. RICHET, J. CROSNIER, D. ALAGILLE, L. COURNOT, J. L. FUNCK-BRENTANO, J. LUBETZKI, M. MASSON, G. MATHÉ, R. NORDMANN and G. POINSARD; Preface by PASTEUR VALLERY-RADOT. 360 pages; 25 × 16 cm. 1954. Éditions Médicales Flammarion, Paris. Price, 2.600 francs.

A Textbook of Neurology. By H. HOUSTON MERRITT, M.D., Professor of Neurology, Columbia University, etc. 746 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $12.50.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. Endokarditis Erworbene Klappenfehler Phonokardiographie. By PROF. DR. RUDOLF THAUER. 408 pages; 23 × 15.5 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, kart. DM 48.–

COLLEGE NEWS NOTES

New Life Members

It is a sincere pleasure for the College to announce that the following Fellows have become Life Members since the publication of the list in the February issue of this journal:

Dr. Clifford J. Barborka, Chicago, Ill.
Dr. Joseph Budnitz, Pittsfield, Mass.
Dr. James F. Faulkner, Boston, Mass.
Dr. Claude E. Forkner, Boston, Mass.
Dr. Arthur Bliss Dayton, New Haven, Conn.
Dr. Bernard H. Berman, Washington, Pa.
Dr. Richard E. Gordon, New York, N. Y.
Dr. Joseph W. Gardam, Newark, N. J.
Dr. Marion E. Howard, New Haven, Conn.
Dr. John R. Haserick, Cleveland, Ohio

Gifts to College Library of Publications by Members

The College is indebted to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

Menard M. Gertler, M.D., F.A.C.P., New York City, and Paul D. White, M.D., M.A.C.P., Boston, Mass.—*Coronary Heart Disease in Young Adults—A Multidisciplinary Study.*

Roscoe L. Pullen, M.D., F.A.C.P., Columbia, Mo.—*Pulmonary Diseases.*

John Russell Twiss, M.D., F.A.C.P., and Elliot Oppenheim, M.D., F.A.C.P., New York City—*Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract.*

Richard M. Burke, Lt. Col., (MC), AUS, F.A.C.P., Denver, Colo.—*An Historical Chronology of Tuberculosis* (2nd Edition).

Meetings, A.C.P. Committee on Credentials

The Committee on Credentials of the American College of Physicians is meeting in Philadelphia, March 19–20 and April 23, the latter meeting immediately preceding the 36th Annual Session.

The next succeeding meeting at which proposals of new members will be acted upon will be held Nov. 11–12, 1955, at the College Headquarters. All proposals to be acted on at these meetings must be received at College Headquarters sixty days in advance of these dates. Governors may require that proposals be in their hands ninety days before the meeting.

Report on American College of Physicians' Insurance Plans

On April 15 of this year the Health and Accident Insurance Plan will be two years old. As of this date (Feb. 1) there has been paid out a total of $264,244.04 to 644 members of the A.C.P. Of this number 9 have been receiving benefits for over one year, and it looks as though these claims will run the full 5 years, for which benefits are now payable under the Plan.

Certificate No. 3746 has just been issued. Looking at the number of members insured and the number of claims received to date, it would seem that a member of

the A.C.P. has a little better than a six-to-one chance of needing Health and Accident protection in a two-year period. Those members that have not taken advantage of the benefits of this plan should keep this fact in mind. Applications to participate will be gladly and promptly sent, upon request to the Association Service Office, 1500 Walnut St., Philadelphia 2, Pa.

Claims are now being received at the rate of approximately $20,000.00 per month. In most cases the checks in payment are in the mail within 24 hours from the time the completed forms are received.

Extension of Benefits Plan. By the time you read this report, members should have received notice and application to participate in the newly approved five-year extension of sickness benefits recently offered by the Educators Mutual Insurance Co. These benefits are available only to members who have first applied for our basic plan. The rates for the increased coverage are as follows:

$50.00 per week—$25.00 additional premium
75.00 per week— 37.50 additional premium
100.00 per week— 50.00 additional premium

Members who have been insured are granted the opportunity to subscribe if their application is completed and mailed on or before April 15. About 1,500 of our presently insured members requested this added benefit. To them this special notice is particularly addressed. It is hoped that their applications will be forwarded by return mail.

To the members who have not yet subscribed to the A.C.P. Health and Accident Insurance Plan, here is an added incentive to do so. This plan is now more liberal than any such plan offered to any national association, and at exceptionally attractive rates. This group is going to be given the period from April 15 to June 1 to apply for our basic plan and at the same time secure the five-year Extended Sickness Benefit. Many in this group said they would join the plan when the period of payment for sickness benefits was extended. Their attention is called to the fact that they are now being offered these increased payments in accordance with their request. Their applications will be expected.

If anyone has any questions, write to the Association Service Office so that the desired information may be supplied.

Malpractice. The members of the A.C.P. are proving in fact that they are really a preferred risk. Our plan has now been in force for two years and one month. During all that time only fourteen incidents have been reported that could have developed into claims. Of these, only three have turned into actual claims on which payments have been made. One was for $5,000.00, one for $20.00, and the third for $10.95. There are four notices of incidents not yet settled, but it is expected that they will be closed at an early date with no payment necessary.

Only 1,246 members have secured this protection through the A.C.P. Group Plan. About 40 to 50 new applications are coming in each month. Further reduced rates cannot be secured until 50% of our practicing members have joined this plan. It is recommended that *all* members who have not already joined forces under the A.C.P. Plan do so when next their Malpractice Insurance comes up for renewal.

As an aid to demonstrate clearly the advantage of the A.C.P. rates, individual comparisons for each State are now being mailed to each member. It is hoped that this will be complete by May 1.

During the past six months Dr. Chaney, Chairman of the Insurance Committee, has been busy securing the lowest quoted rates in each State. These rates have been compared with those offered under the A.C.P. Plan and the comparison forms mailed to each member.

Dread Disease. There have been 1,295 certificates issued covering members and their families under this plan. There are a number of claims in process of payment.

The anniversary date is June 1, 1955. Shortly following that date a report of first-year payments will be made. It is evident, however, that this plan has been of great help to a number of members. It will be open for subscription again on May 15 for certificates to be effective June 15. If this type of coverage is necessary for your family, be sure to secure it on the next open subscription date.

A. C. P. Regional Meetings

Schedule from March 1, 1955:

Utah, at Salt Lake City, March 5, 1955
Kansas, at Wichita, March 18, 1955
Southern Illinois, at Peoria, March 19, 1955
Tennessee, at Chattanooga, April 11, 1955
North Dakota, at Jamestown, September 10, 1955
Midwest (Ill., Ind., Iowa, Wis.), at Madison, Wis., October 15, 1955
New Jersey, at Newark, November 2, 1955

Abstracts of Articles in Annals to Be Published in Interlingua Beginning July 1, 1955

By action of the Editorial Board of the Annals of Internal Medicine, with the approval of the Board of Regents of the American College of Physicians, beginning July 1, 1955, an abstract of each paper will be published in Interlingua. It is proposed to publish these abstracts at the end of each article. Each author who has his paper accepted for publication shall furnish an abstract of the paper, as a condition to acceptance of his manuscript for publication. Interlingua is the new international scientific language.

Forthcoming Meetings of Medical Interest

The following annual meetings have been scheduled by the societies designated:
The American Academy of General Practice:

1955: March 28–31, Los Angeles
1956: March 18–23, Washington, D. C.
1957: March 25–28, St. Louis

The American Goiter Association:

1955: April 28–30, Oklahoma City

The Royal College of Physicians and Surgeons of Canada:

1955: Oct. 21–22, Quebec City, P. Q.
1956: Oct. 26–27, Toronto, Ont.
1957: Oct. 18–19, Montreal, P. Q.

A.C.P. Activities in Hawaii

Under the Governorship of Dr. Nils P. Larsen, F.A.C.P., three dinner meetings of the Hawaiian members of the College have been held during the past year, one during February, 1954, one during June, 1954, and one on February 10, 1955. The last program was developed on the subject of Hypertension. Most of the members in Hawaii were present at these meetings and there were usually one or two visitors or prospective candidates in attendance.

The Fifth Annual Institute in Psychiatry and Neurology, sponsored by the Veterans Administration Hospital, Lyons, N. J., The New Jersey Neuropsychiatric Association, and the New Jersey District Branch of A.P.A., will be held on Wednesday, April 13, 1955, at the Veterans Administration Hospital, Lyons, New Jersey. Additional information may be obtained from Crawford N. Baganz, M.D. Manager.

Demonstration of the Clinical Management of Poliomyelitis

Baylor University College of Medicine, Southwestern Poliomyelitis Respiratory Center and Jefferson Davis Hospital in coöperation with the National Foundation for Infantile Paralysis, Inc. announce a three day and two evening postgraduate course on the clinical management of poliomyelitis, on April 19, 20 and 21, 1955.

The course is designed for physicians, nurses, medical social service workers, physical and occupational therapists to cover complete care of poliomyelitis with emphasis on the severely involved patient, the physician's responsibility in the effective coordination of auxiliary services, and the value of comprehensive care.

Address applications to: William A. Spencer, M.D., Medical Director, Southwestern Poliomyelitis Respiratory Center, Jefferson Davis Hospital, 1801 Buffalo Drive, Houston 3, Texas.

Troisieme Reunion des Endocrinologistes de Langue Francaise

This meeting of French speaking endocrinologists will take place in Brussels on June 18, 19 and 20, 1955.

The morning sessions will be devoted to the reading of the reports, the afternoon sessions to discussions relating to the problems raised by the reports. *First day:* The hormonal equilibrium of gestation; *second day:* Androgens in the female; *third day:* Certain problems of cortisone therapy.

Registration: Applications may be forwarded to Professor J. Lederer, secretary to the Congress, 233, avenue de Tervueren, Brussels.

The registration fee is fixed at 800 Belgian francs or $16, payable in Belgian francs at the "compte chèque-postal n° 624.794 de la Société belge d'Endocrinologie, compte congrès" or in foreign currency by checks addressed to Professor J. Lederer, 233, avenue de Tervueren, Brussels.

Postgraduate Course in Allergy

A Postgraduate Course in Allergy on the "Modern Management of Allergic Diseases" will be given at The Institute of Allergy of The Roosevelt Hospital, New York City, from May 9 to 20, 1955. The fee for the course is $150.00. Enrollment is limited and those desiring information should write to Robert A. Cooke, M.D., 429 W. 59th St., New York 19, N. Y.

First Pan-American Congress on Rheumatic Diseases under the auspices of the Pan-American League Against Rheumatic Diseases with Brazilian Rheumatism Society as host, will be held in Rio de Janeiro and Sao Paulo, Brazil, August 14–20, 1955. For further information write Dr. Waldemar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio de Janeiro, Brazil, South America.

Dr. William S. Middleton, M.A.C.P., Appointed Chief Medical Director of the Veterans Administration

Dr. William S. Middleton, M.A.C.P., former Regent and former President of the American College of Physicians, has been appointed the Chief Medical Director of the Veterans Administration, to assume duty on March 1, 1955. Vice Admiral Joel T. Boone, who has been in Government Service 41 years, has announced his resignation and retirement due to ill health.

Dr. Middleton graduated from the University of Pennsylvania School of Medicine in 1911, and served his internship at the Philadelphia General Hospital. In 1912 he joined the staff of the University of Wisconsin Medical School as an Instructor in Clinical Medicine. He received rapid promotions until he became Dean of the Medical School in 1935. He is now retiring from this position. He served as a Medical Officer with the American Expeditionary Forces in France during the First World War and was the Chief Medical Consultant to the U. S. Army in the European Theater during the Second World War, with the rank of Colonel. He made outstanding contributions to the American College of Physicians as a Regent for several years and later as its President in 1950–1951.

Dr. Theodore G. Klumpp, F.A.C.P., New York City, Chairman of the Hoover Commission's Task Force on Medical Services, has recently been appointed a member of the National Advisory Council on Vocational Rehabilitation, a new Federal agency organized to restore the nation's handicapped to useful lives. President of Winthrop-Stearns Inc., Dr. Klumpp is also a Director of the World Medical Association and the Commission on Chronic Illness and for five years was Chief of the Drug Division, U. S. Food and Drug Administration.

Col. Philip W. Mallory, (MC), USA, (Associate), has been appointed Chief of the Medical Information and Intelligence Division, Office of The Army Surgeon General. This new Division will continue the functions of the former Medical Intelligence Branch, and at the same time, will assume the additional duties of supervising the security functions of the Office of The Surgeon General and of providing medical information on foreign areas to authorized individuals and agencies. Prior to his present assignment Col. Mallory served with the Joint Brazil-U. S. Military Commission in Brazil.

Dr. Donal R. Sparkman, F.A.C.P., Seattle, Wash., was presented a citation for outstanding service from the President's Committee on Employment of the Physically Handicapped. The citation was "in recognition of his outstanding efforts expended in promoting equal opportunity in employment for the physically handicapped."

Drs. Louis H. Bauer, F.A.C.P., New York City, and Tom D. Spies, F.A.C.P., Birmingham, Ala., were among those honored in December by the Cuban National College of Medicine. They received scrolls making them honorary members of the College. The presentations were made by Dr. Augusto Fernandez Conde, President of the National College, and were presented on the anniversary of the birth of Dr. Carlos J. Finlay, Cuban scientist, on Dec. 3, 1954.

Dr. William A. Shepherd, F.A.C.P., Richmond, has become a member of the Fifty Year Club of the Medical Society of Virginia. A graduate of the Class of 1904 at the Medical College of Virginia, Dr. Shepherd has been a Fellow of the American College of Physicians since 1920 and is Pathologist at the Johnston-Willis Hospital.

Dr. Howard K. Petry, F.A.C.P., resigned on December 16, 1954, as Superintendent of the Harrisburg (Pa.) State Hospital. He had completed 33 years as a medical and administrative officer of the Mental Health System and 20 years and 10 months as Superintendent of the Hospital. The last building completed under his administration, the admission unit, has been named in his honor, "The Petry Building."

Dr. Petry is conducting a consultation practice in Psychiatry at 2800 N. Second St., Harrisburg, Pa., and is Chief of the Psychiatric Service at the Harrisburg Hospital.

Dr. Hamblen C. Eaton, F.A.C.P., former Clinical Director at the State Hospital, has succeeded Dr. Petry as Superintendent.

Dr. Anton J. Carlson, M.A.C.P., Chicago, was the guest of honor at a dinner held on his eightieth birthday, Jan. 29, at the University of Chicago. Frank P. Hixon Distinguished Service Professor, Emeritus, at the University of Chicago, Dr. Carlson is President of the National Society for Medical Research, the Research Council on Problems of Alcohol, and the Chicago Committee on Alcoholism. Dr. Carlson has been awarded honorary degrees by eight academic institutions and has been a Master of the College since 1948, having been elected a Fellow in 1926.

Dr. John W. R. Norton, F.A.C.P., Raleigh, N. C., was recently elected President of the Association of State and Territorial Health Officers.

Dr. W. Edward Chamberlain, F.A.C.P., Professor of Radiology at Temple University School of Medicine, was installed as President of the Philadelphia County Medical Society on Jan. 12.

Dr. Albert Aranson (Associate), Portland, has been elected Vice President of the Maine Trudeau Society.

Dr. Lewis B. Flinn, F.A.C.P., Wilmington, was recently installed as President of the Medical Society of the State of Delaware.

During the Tri-State Medical Meeting, held Feb. 21–22 at Old Point Comfort, Va., Dr. Paul D. Camp, Jr., F.A.C.P., Richmond, Va., was installed as President.

Dr. Max K. Newman, F.A.C.P., Detroit, was recently reëlected Secretary-Treasurer of the American Society of Physical Medicine and Rehabilitation.

Dr. A. McGehee Harvey, F.A.C.P., Baltimore, has recently been appointed Recorder of the Association of American Physicians. He succeeds Dr. Cecil J. Watson, F.A.C.P., Minneapolis.

Dr. William D. Paul, F.A.C.P., Iowa City, was recently elected President of the American Congress of Physical Medicine and Rehabilitation. Other officers include Dr. Howard A. Rusk, F.A.C.P., New York City, President-Elect; Dr. Alvin B. C. Knudson, F.A.C.P., Washington, D. C., a Vice President; Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., Treasurer; and Dr. Walter J. Zeiter, F.A.C.P., Cleveland, Executive Director.

Dr. Warren W. Moorman (Associate), Fort Worth, has recently been elected Secretary-Treasurer of the Texas Rheumatism Association.

Dr. Charles L. Brown, F.A.C.P., Philadelphia, will resign on July 1 as Dean of Hahnemann Medical College and Hospital of Philadelphia to become the first Dean of the newly organized Seton Hall College of Medicine, Jersey City, N. J. Dr. Brown has been Dean at Hahnemann since 1946 and is currently serving as Consultant to Seton Hall.

Dr. William D. Stroud, F.A.C.P., Treasurer of the American College of Physicians, Philadelphia, left on Feb. 14, 1955, for a trip around the world. Under the auspices of the Philippine Heart Association, he will deliver a series of lectures in the Philippine Islands. While there he will be a guest of the President of the Philippines at Malacanang Palace and make visits to the University of Santo Tomas College of Medicine. He will address a Joint Meeting of the Manila Medical Society and the University of Santo Tomas Medical Association. He will also be the guest speaker at a Joint Meeting of the Philippine College of Physicians and the University of the Philippines Physicians Association. He proposes to continue his journey to Hong Kong, Delhi, Istanbul, Athens, Rome and to Paris, returning about the middle of March to Philadelphia.

Dr. Edward L. Turner, F.A.C.P., Chicago, Secretary of the A.M.A. Council on Medical Education and Hospitals, discussed "The Administration Viewpoint" under the general heading of "The Teaching of Radiology to Medical School Undergraduates" at the 22nd Annual Conference of Teachers of Clinical Radiology. The meeting was held Feb. 12 in Chicago under the auspices of the Commission on Education of the American College of Radiology.

Dr. Harris Isbell, F.A.C.P., Director of the Addiction Research Center at the U. S. Public Health Service Hospital, Lexington, Ky., spoke on "The Medical Aspects of Drug Addiction" at a meeting of the New York Academy of Medicine, Feb. 3.

Dr. Frank L. Engel, (Associate), Durham, N. C., discussed "The Clinical and Metabolic Significance of Ketosis with Particular Reference to Diabetes" at a meeting of the Alameda-Contra Costa Medical Association on Jan. 31 in Oakland, Calif.

Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Mich., addressed the Rochester (N. Y.) Academy of Medicine on Feb. 1. His subject was "Endocrine and Metabolic Aspects of Man's Responses to Stressing Circumstances."

A Symposium on Diabetes was presented Jan. 18 under the sponsorship of the Section on Medicine of the New York Academy of Medicine. The Symposium reported the results of studies made at the New England Deaconess Hospital, Boston. Those on the Symposium included Drs. Howard F. Root, F.A.C.P., Priscilla White, F.A.C.P., and Alexander Marble, F.A.C.P. Dr. White spoke on "Pregnancy in Diabetes: Results of Recent Experience" and "Attempts to Alter the Trend of Diabetes in Young Patients: Preliminary Report." Dr. Marble spoke on "Experience with Lente Insulin," and Dr. Root discussed "Cost of Treatment and Rehabilitation of Patients with Foot Lesions, A Coöperative Study of 500 Cases in Boston Hospitals, 1953–1954."

Dr. Charles A. Doan, F.A.C.P., Columbus, College Governor for Ohio, discussed "The Differential Diagnosis and Management of the Lymphomata" on Jan. 11 at the Henry Ford Hospital, Detroit.

Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., presented "Which Goiters Should Be Treated Surgically and Which with Radioactive Iodine" at a meeting of the Wayne County Medical Society at Wayne University College of Medicine, Detroit, Jan. 10.

Dr. Paul B. Beeson, F.A.C.P., New Haven, Conn., Ensign Professor of Medicine at Yale University School of Medicine, will speak on "The Movement of Microorganisms in the Host's Tissues" at the Maimonides Hospital of Brooklyn on April 21 at 8:30. His paper will constitute the Third Annual Emanuel B. Schoenbach Memorial Lecture and will be delivered in the Hospital's Solarium.

Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz., spoke on "Treatment of Rheumatoid Arthritis" as a guest of the Medical Society of Milwaukee County on Jan. 13.

Drs. Henry L. Bockus, F.A.C.P., Philadelphia, and Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York, were among the guest speakers at the Sixteenth Annual Clinic Day, Jan. 26, at Mount Carmel Mercy Hospital, Detroit. Their respective subjects were "Functional Disorders of the Digestive Tract" and "Cerebral Vascular Diseases."

Ten members of the College contributed to the 51st Annual Congress on Medical Education and Licensure, held in Chicago, Feb. 5–8. Dr. Walter L. Bierring, M.A.C.P., Des Moines, Iowa, participated in panel discussions on "The Problem of Foreign Medical Graduates" and "Proposed Program for the Evaluation of Graduates of Foreign Medical Schools." As Secretary-Treasurer of the Federation of State Medical Boards of the United States, Dr. Bierring delivered the "Report of the Secretary-Treasurer and Editor of the *Federation Bulletin*." Dr. George Morris Piersol, M.A.C.P., Philadelphia, Dean of the University of Pennsylvania Graduate School of Medicine, spoke on "The Use of Formal Didactic Training in Graduate Medical Education." Dr. John Z. Bowers, F.A.C.P., Salt Lake City, Dean of the University of Utah College of Medicine, was moderator for a panel on "Costs and Financing of Postgraduate Medical Television." Drs. Walter E. Vest, F.A.C.P., Huntington, W. Va., and S. M. Poindexter, F.A.C.P., Boise, Idaho, participated in the panel on "Essentials of a Modern Medical Practice Act. Report of the Study Committee." Dr. Samuel A. Levinson, F.A.C.P., Chicago, opened the discussion of "Scientific Medicolegal Investigation." Drs. Harold J. Jeghers, F.A.C.P., Washington, D. C., and John J. Butler (Associate), Rochester, N. Y., were two of the three coauthors of "An Experiment in Making the Hospital a Graduate Medical Center—A Preliminary Report." In a Symposium on The Future of the Internship, moderated by Dr. Franklin D. Murphy, F.A.C.P., Lawrence, Chancellor of the University of Kansas, Dr. Ford K. Hick, F.A.C.P., Chicago, discussed the role of "The Non-Affiliated Hospital."

Dr. Samuel Mirsky, F.A.C.P., President of the Ottawa Academy of Medicine, delivered the Address of Welcome at the Eighteenth Annual Meeting of the Canadian

Association of Radiologists, held in Ottawa, Jan. 10–12. Among the speakers and their contributions to the scientific program were Dr. Carlton B. Peirce, F.A.C.P., Montreal, "Chondrodystrophy: Fetal Manifestations and Post-natal Progression"; Dr. T. L. Fisher, F.A.C.P., Ottawa, "Comments on Medico-Legal Trends"; and Dr. Victor Szyrynski (Associate), Ottawa, "Calcification of the Basal Ganglia."

A Weight-Control Colloquium was held Jan. 18–20 at Ames under the sponsorship of the Iowa State College. Among the speakers were Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., who discussed "Aging as a Problem of Nutrition" and Dr. Daniel A. Glomset, F.A.C.P., Des Moines, who spoke on "The Role of the Physician in Weight Control." Dr. Norman B. Nelson (Associate), Iowa City, moderated a panel discussion on "Who Should Reduce."

Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, Head of the Department of Internal Medicine at the University of Utah School of Medicine, spoke on "Recent Advances in Hematology" in San Francisco, Jan. 29. His talk was delivered as the inaugural Margaret Beattie Lecture, sponsored by the Council of American Bioanalysts (Western Region) and the California Association of Clinical Laboratories.

Dr. John R. Neefe, F.A.C.P., Philadelphia, spoke on "Hepatitis" at a meeting of the Boston Gastro-enterological Society, held in the Boston City Hospital, Jan. 26.

Drs. William B. Bean, F.A.C.P., Iowa City, and Garfield G. Duncan, F.A.C.P., Philadelphia, were among the guest speakers at the Nineteenth Annual Midwinter Meeting of the International Medical Assembly of Southwest Texas, which met in San Antonio, Jan. 24–26.

Five members of the College participated in the Mid-South Postgraduate Medical Assembly, held in Memphis, Tenn., Feb. 8–11. Speakers and their fields included Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, and Dr. Sara M. Jordan, F.A.C.P., Boston, Medicine; Dr. John H. Lamb, Jr., F.A.C.P., Oklahoma City, Dermatology; Dr. Roy W. Scott, F.A.C.P., Cleveland, and Dr. Arthur J. Merrill (Associate), Atlanta, Medicine.

At the 32nd Annual Meeting of the American Orthopsychiatric Association, held in Chicago, Feb. 28–March 2, Dr. Sydney G. Margolin, F.A.C.P., New York City, was among the participants in the Symposium on Roads to Human Understanding on the Industrial Front.

Dr. Robert Collier Page, F.A.C.P., New York City, President of the Industrial Medical Association and Chief Medical Consultant for the Standard Oil Company of New Jersey, was one of the principal speakers at the Sixth Conference on Alcoholism, sponsored by the Boston Committee on Alcoholism and more than fifty industrial, labor and professional organizations and held in Boston, Jan. 26.

Dr. William H. Beierwaltes, F.A.C.P., Ann Arbor, Mich., was one of the guest speakers at the Annual Postgraduate Course in Radiology, held at the University of Kansas Medical Center, Kansas City, Feb. 14–17. The course was held in conjunction with the annual meeting of the Kansas Radiological Society and the Radiological Society of Greater Kansas City.

Dr. Roger S. Mitchell, F.A.C.P., formerly of the Trudeau-Saranac Institute at Trudeau, N. Y., has moved to Colorado, where he has become Associate Professor of Medicine, in charge of the care and teaching of Pulmonary Diseases at the University of Colorado School of Medicine, and Director of the Colorado Foundation for Research in Tuberculosis. His new address is 4200 E. Ninth Ave., Denver, Colo.

Dr. Alex. M. Burgess, Sr., F.A.C.P., has resigned as Area Chief of Medicine in the Veterans Administration and has been appointed Director of Medical Education at Newport Hospital, Newport, R. I., and Miriam Hospital, Providence. Dr. Burgess, former College Governor, Regent, and Vice President, received the honorary degree of Doctor of Science from Brown University last June.

Dr. Elmer L. Caveny, F.A.C.P., Washington, D. C., was recently appointed Professor of Psychiatry and Chairman of the Department of Psychiatry and Neurology at the Medical College of Alabama, Birmingham.

Dr. Louis H. Clerf, F.A.C.P., former Professor of Laryngology and Bronchoesophagology at Jefferson Medical College of Philadelphia, has recently retired and is now living in St. Petersburg, Fla.

Dr. John G. Ryan, F.A.C.P., Denver, has recently retired from the faculty of the University of Colorado School of Medicine. A graduate of Rush Medical College in 1910, Dr. Ryan was a member of the faculty for 32 years and is now Clinical Professor of Medicine, Emeritus. He was elected to Fellowship in the American College of Physicians in 1928.

"Mead Digest for Residents and Interns" is a new publication put out by the Mead Johnson Company for free distribution among interns and residents. It is slanted directly at the practical problems of getting started in practice which every young doctor faces at the end of his hospital training period. This Digest, along with the Mead Johnson Scholarship Awards for Postgraduate Training, is an integral part of Mead's over-all program of assistance to residents and interns.

CONDENSED TRANSACTIONS—BOARD OF REGENTS, A.C.P.
NOVEMBER 14, 1954

The regular autumn meeting of the Board of Regents of the American College of Physicians convened at the College Headquarters, Philadelphia, November 14, 1954, with President Cyrus C. Sturgis presiding. Present were Dr. George F. Strong, President-Elect, Dr. Marion A. Blankenhorn, 1st Vice President, Dr. Ramon M. Suarez, 3rd Vice President, Dr. William D. Stroud, Treasurer, Dr. Richard A. Kern, Secretary General, Mr. E. R. Loveland, Executive Secretary, and the following Regents: Dr. Edward L. Bortz, Dr. Herbert K. Detweiler, Dr. Harold H. Jones, Dr. Howard P. Lewis, Dr. Dwight L. Wilbur, Dr. Fuller B. Bailey, Dr. Eugene B. Ferris, Dr. Philip S. Hench, Dr. T. Grier Miller, Dr. J. Murray Kinsman, Dr. Asa L. Lincoln, Dr. Walter L. Palmer, Dr. Karver L. Puestow, Dr. Wallace M. Yater and Dr. Maurice C. Pincoffs. Additionally, the following Committeemen, other than Regents, were in attendance: Dr. Lowell T. Coggeshall, Chairman of the Committee on Latin-American Fellowships; Dr. George Morris Piersol, Chairman of the Committee on Credentials; Dr. William C. Chaney, Chairman of the Committee on Insurance and Chairman of the Reference Committee on Blue Shield and Prepaid Insurance Plans; Dr. Thomas M. McMillan, Chairman of the Committee on Postgraduate Courses; Dr. Howard Wakefield, Chairman of the Residency Review Committee; Dr. Rudolph H. Kampmeier, Governor for Tennessee; Dr. Elbert L. Persons, Governor for North Carolina, and Dr. LeRoy H. Sloan, Dr. Alex. M. Burgess; Dr. Kenneth B. Babcock and Dr. John Hinman of the Joint Commission on Accreditation of Hospitals, and Dr. LeRoy H. Sloan, A.C.P. Commissioner on the Joint Commission on Accreditation of Hospitals.

The appointment of Dr. Robert Friedenberg as interim College Governor for New Mexico, as made by the President, was confirmed.

By formal resolution the Board of Regents referred back to the Council on Medical Education and Hospitals and the Advisory Board of the Medical Specialties, with a favorable endorsement, a proposal concerning the establishment of certifying boards which concern individuals who do not have M.D. degrees, but have Ph.D. degrees, as for instance, the microbiologists, clinical pathologists, and others.

By formal resolution, provision was made for the adoption of an official academic robe of the College, said robe to be worn by the President at the Convocation, the robe to become the property of the President on his retirement from office. (This action was later rescinded by action of the Executive Committee, so far as the 36th Annual Session, 1955, is concerned, with directions for further deliberations as to whether it shall be an official robe for all the Regents of the College on the occasion of the Convocation.)

A somewhat extended report on the activities of the Joint Commission on Accreditation of Hospital was made by Dr. Alex. M. Burgess and Dr. LeRoy H. Sloan, A.C.P. Commissioners, supplemented by reports from the Director, Dr. Kenneth B. Babcock, and Dr. John Hinman, heretofore A.C.P. Hospital Inspector with the Commission. Points clearly brought out were: that the Board of Regents should appreciate more the importance of the job of hospital accreditation; that the College should more actively participate in the work of the Commission and that more field representatives who are men of mature judgment and are qualified internists should be added to the Commission staff; that the College should take the necessary steps to formulate the criteria for certification that shall apply to the Department of Internal Medicine in hospitals.

A resolution was adopted, providing that the President shall appoint an Advisory Committee to the Joint Commission, said Committee to be composed of qualified leaders in Internal Medicine, its function to be the development of basic principles,

standards and concepts which shall accomplish the necessary emphasis on medicine. (The President later appointed to this Committee, Dr. Arthur R. Colwell, Sr., Chicago, Chairman, Dr. Charles W. Eisele, Denver, Dr. Eugene B. Ferris, Atlanta, Dr. J. Murray Kinsman, Louisville, and Dr. E. Hugh Luckey, New York.)

Dr. Howard Wakefield, Chairman of the Residency Review Committee, reported at length on the work of that Committee, in connection with certification of hospitals for approved residency training, his report dealing with policy relating to residency training in Veterans Administration Hospitals, requirements for approval of residency training programs in Internal Medicine, and admission of graduates of foreign medical schools.

A brief report was received, and spread upon the Minutes, from the Chairman of the American Board of Internal Medicine, Dr. Walter L. Palmer.

After extended discussion, in which all members of the Board joined, it was voted that no action be taken on a proposal to abolish Associateship, said proposal having emanated from the Committee on Membership and the Board of Governors at the 1954 Session.

The Secretary General reported the deaths of 55 Fellows and 4 Associates since the last meeting of the Board, said names and dates of demise being spread upon the Minutes. The Secretary General was instructed to prepare a resolution in the case of Dr. Charles F. Moffatt, former Governor and former Regent of the College, now deceased, to be spread upon the Minutes, a copy to be sent to Dr. Moffatt's widow and son. Secretary General Kern further reported 14 additional Life Members, making a grand total of 1,251, of whom 130 have died, leaving a balance of 1,121.

The Executive Secretary's report revealed an increase in the number of candidates for Associateship during 1954 of over 11%, a slight decrease in the number of candidates for Fellowship; a registration of 1,313 physicians in A.C.P. Postgraduate Courses during 1954, an increase of 38% over the previous year; an increase during 1954 in the circulation of the ANNALS OF INTERNAL MEDICINE of more than 1,000; a gross income of nearly $100,000.00 from advertising in the ANNALS; the holding of 23 Regional Meetings during 1954; the conduct of two surveys, one being an evaluation of the Annual Session program of 1954 and one of the experimental television symposium conducted by the College on September 23, 1954.

By formal resolution, the Executive Secretary was instructed to revise and republish the Directory of the College during 1955, the pre-publication price to members for the same to be $6.00; the post-publication price, $7.00.

Dr. William D. Stroud, Treasurer, reported the present cash value of investments held by the College as $1,337,231.00, the cost or book value, $1,068,092.00; appreciation, $269,139.00. Income from securities had been approximately $43,000.00 for the year; average yield, 3.71%.

Dr. George Morris Piersol, Chairman, presented the report of the Committee on Credentials. Growing out of its recommendations, 327 candidates were elected to Associateship and 118 candidates were elected to Fellowship. (The list was published in the December, 1954, Issue of this Journal.) The principle was reiterated by the Committee on Credentials and the Board of Regents that unless a candidate shall be a man of great distinction, internationally known, he should first enter the College through the usual procedure of election to Associateship. The Committee reported that it had adopted a plan of far more investigation than usual, in the case of candidates proposed for Direct Fellowship, this plan involving the distribution of a special inquiry card to all the Fellows of the College in their immediate areas.

Dr. Lowell T. Coggeshall, Chairman of the Committee on Latin-American Fellowships, made a detailed report on the meetings and transactions of that Com-

mittee. The following new Latin-American Fellows had been approved and were currently pursuing their fellowships in the United States:

1. Dr. Alfredo Ramiro BASTO, Maceio, Alagoas, Brazil, S. A.
2. Dr. Renato Piza de Souza CARVALHO, Sao Paulo, Brazil, S. A.
3. Dr. Amaury Domingues COUTINHO, Recife, Pernambuco, Brazil, S. A.
4. Dr. Jorge A. FERNANDEZ Mendia, Guatemala City, Guatemala, C. A.
5. Dr. Jacques HOULI, Rio de Janeiro, Brazil, S. A.
6. Dr. Luis LANDA Verdugo, Mexico, D. F.
7. Dr. Luis Carlos MAAS, Asuncion, Paraguay, S. A.
8. Dr. Radi MACRUZ, Sao Paulo, Brazil, S. A.
9. Dr. Guillermo PORRAS Garcia, Managua, Nicaragua, C. A.
10. Dr. Jayme ROZENBOJM, Sao Paulo, Brazil, S. A.
11. Dr. Augusto SCHUSTER Cortes, Santiago, Chile, S. A.
12. Dr. Juan Ivica SERKOVIC Lujak, Miraflores, Lima, Peru, S. A.

Dr. Coggeshall reported also that 38 individuals from 14 different Latin-American and Central American countries have completed their fellowship training, distributed among the following countries: Colombia, 3; Brazil, 4; Chile, 11; Argentina, 1; Peru, 2; Venezuela, 1; Costa Rica, 2; El Salvador, 1; Mexico, 7; Puerto Rico, 1; Uruguay, 1; Guatemala, 1; Ecuador, 1; Paraguay, 2. 22 are still in training, distributed from the following countries: Peru, 3; Brazil, 8; Paraguay, 3; Guatemala, 1; Chile, 5; Mexico, 1; Nicaragua, 1. Dr. Coggeshall pointed out that the men who have completed these fellowships are playing a major role in medical education in their own countries; 4 are Professors of Medicine, 1 an Associate Professor of Medicine, 11 Assistant Professors of Medicine and 9 Instructors; only 2 give no formal affiliation with teaching instructiors and they came from a country where there is no medical school. The Committee had personally interviewed each of the current fellows, determining upon their current progress and their future interest and needs with regard to Preceptors. The Committee was taking appropriate action to select Preceptors for the current fellows and to organize their programs in the United States.

Dr. George Morris Piersol, Chairman, presented the report of the Committee on Advertising and Commercial Exhibits, noting that the pages of paid advertising for 1954 will show an increase of 37.6% over 1953, and that the gross advertising income for 1954 will approximate $112,000.00, compared with $74,500.00 in 1953. The Committee noted material improvements in the redesigned cover and the new 55# coated paper stock used in the Journal, and approved the adoption of "standard colors" for use in the Advertising Section. Dr. Piersol explained in some detail the work of the Committee, with regard to the acceptance and rejection of various advertisements and exhibits.

Dr. Asa L. Lincoln, Chairman, presented the report of the Committee on Public Relations, covering numerous communications. As a result of the recommendations of the Committee, dues of several incapacitated members were waived until their recovery and resumption of practice, one Associate was dropped, and one Associate's resignation was accepted.

Dr. T. Grier Miller, Chairman, reported for the Committee on Fellowships and Awards. Growing out of the recommendations of that Committee, the Board of Regents awarded Research Fellowships for the year 1955–56 to the following:

1. *Dr. Thomas T. Amatruda, Jr.*
   Age, 28; a graduate of Yale University School of Medicine, 1951; to work under Dr. Frank L. Engel, Duke University School of Medicine, Durham, N. C., on a study of the hormonal control of fat metabolism.

2. *Dr. John Edmund Bethune*
   Age, 27; a graduate of Dalhousie University Faculty of Medicine, 1953; to work under Dr. George W. Thorn, Peter Bent Brigham Hospital, Boston, Mass., on the relationship of the chemical structure of adrenal steroids to physiological action in man.
3. *Dr. David Morris Kipnis*
   Age, 27; a graduate of the University of Maryland School of Medicine, 1951; to work under Dr. Carl Cori, Professor of Biochemistry, Washington University School of Medicine, St. Louis, Mo., on the defect in fatty acid metabolism associated with diabetes mellitus.
4. *Dr. Dan Anderson Martin*
   Age, 28; a graduate of Harvard Medical School, 1952; to work under Dr. Kerr L. White and Dr. David P. Jones, University of North Carolina School of Medicine, Chapel Hill, N. C., on a study of the influence of adverse life situations and emotions on the precipitation and exacerbation of congestive heart failure.
5. *Dr. Calvin Alpheus Stanfield*
   Age, 27; a graduate of the University of Rochester School of Medicine, 1953; to work under Dr. Herbert R. Morgan, Department of Bacteriology, University of Rochester School of Medicine, Rochester, N. Y., on a study in tissue culture the delayed (tuberculin) type of hypersensitivity characteristic of streptococcal and tuberculous infections.
6. *Dr. Albert I. Winegrad*
   Age, 28; a graduate of the University of Pennsylvania School of Medicine, 1952; to work under Dr. A. Gorman Hills, Hospital of the University of Pennsylvania, Philadelphia, Pa., on proposed investigations in the physiology and pathophysiology of the adrenal cortex.

The following candidate, *Dr. Thomas T. Amatruda, Jr.,* was selected from the above group to be designated as the "Alfred Stengel Research Fellow," on account of his outstanding qualifications.

The A. Blaine Brower Traveling Scholarships were awarded to the following:

1. Dr. Robert W. Frelick, Wilmington, Del.
2. Dr. C. T. Hagan, Wichita, Kans.

The Elizabeth Archbold Bowes Traveling Scholarship, restricted to Canada, was awarded to Dr. Judah L. Guravich, St. John, N. B., Canada.

The three Mead Johnson Postgraduate Scholarships were awarded to:

1. Dr. Albert Reginald Cox (nominated by Governor H. A. DesBrisay, British Columbia)
2. Dr. Allan Louis Forbes (nominated by Governor Charles M. Caravati, Virginia)
3. Dr. Donald L. Rasmussen (nominated by Governor T. C. Bauerlein, Utah)

The John Phillips Memorial Award in Internal Medicine for 1955 was awarded to Dr. George W. Thorn, Boston, Mass. The James D. Bruce Memorial Award in Preventive Medicine for 1955 was awarded to Sir Howard Walter Florey, Oxford, England.

The Committee, through the Executive Offices of the College, had been engaged in a follow-up of past Research Fellows, and out of 48 such Fellows, reports were in hand on 42. Reports received thus far were turned over to Dr. George F. Strong

for analysis before the 1955 Annual Session. The Graduate School of Medicine of the University of Pennsylvania, and other recognized postgraduate medical schools, were approved as training sites for Mead Johnson Postgraduate Scholars. The Committee prescribed, with the approval of the Regents, that in the future the Brower and the Bowes Traveling Scholarship candidates and the Mead Johnson Postgraduate Scholarship candidates shall provide three or more references from qualified persons, including the Governors of the College in their particular areas, thus to aid the Committee in the selection of future awardees. The Committee also reported the establishment of the Willard O. Thompson Memorial Traveling Scholarship Fund, which will be available for awards as soon as the capital has reached $10,000.00. Stipends for the American College of Physicians' Research Fellowships were increased to the following amounts: unmarried fellows, $3,300.00 annually; married fellows, $3,900.00, with an additional allowance of $300.00 for each dependent child, not exceeding two; $500.00 additional to the above amounts to the Alfred Stengel Research Fellow.

Dr. Maurice C. Pincoffs, Chairman, presented the report of the Committee on Masterships. The following nominees were formally elected Masters, in recognition of their positions of eminence and influence and their distinguished contributions to medical knowledge and medical education:

Dr. David P. Barr, New York, N. Y.
Dr. William J. Kerr, Blue Lake, Calif.
Dr. Paul D. White, Boston, Mass.

The following resolution, presented by the Committee on Masterships, was adopted: "To further more continuity in policy, the Committee on Masterships recommends that appointments to this Committee in the future be for a three-year term, and that the appointees be so staggered that only one new member shall be appointed annually; the personnel of the Committee to be, as heretofore, two Regents and one Governor." On the nomination of the Committee on Masterships, and approved by the Board of Regents, Dr. George W. Pickering, Professor of Medicine, St. Mary's Hospital College of Medicine of the University of London, was elected an Honorary Fellow.

Dr. Philip S. Hench, Chairman, presented the report of the Committee on the Alfred Stengel Memorial Award, including the nomination of four candidates. The name of the recipient, unanimously selected by the Regents, will be announced at the Convocation of the College at Philadelphia on April 27, 1955.

Dr. Thomas M. McMillan, Chairman, presented the report on the Postgraduate Course program of the College, announced that over 1,300 physicians had pursued A.C.P. courses during 1954. He then presented the schedule of proposed courses for the spring of 1955, along with a tentative schedule for the autumn of 1955. His proposals and report were unanimously approved. (These schedules have already been published in this Journal and are not herewith repeated.)

Dr. Herbert K. Detweiler, Acting Chairman in the absence of Dr. A. B. Brower, presented the report of the Committee on Finance, which included a review of the operating statements for 1954, security transactions for the Endowment and General Funds, and budgets for the year 1955. Each item was carefully considered and analyzed, and the operating statements and proposed budgets were approved.

Dr. William C. Chaney, Chairman, presented an interim progress report of the Committee on Insurance and the Reference Committee on Blue Shield and Other Prepaid Insurance Plans. Essential data concerning the Group Insurance Plans for members of the College were as follows: Health and Accident: 3,653 certificates outstanding; 559 claims paid, amounting to $229,000.00. Malpractice; 1,068 certificates issued, 1 claim of $5,000.00 paid. Dread Disease: 1,244 certificates issued; 7 claims, 6 for poliomyelitis and 1 for encephalitis; two claims settled in full. It was announced

that several new diseases had been added to the Dread Disease Policy, without additional premium charge, for which notifications were being issued to each certificate holder. Because of the favorable experience in the College Group Plan, covering Health and Accident, five years additional coverage has been made available to certificate holders at their option.

Dr. Chaney then presented a progress report for the Committee on Blue Shield and Other Voluntary Prepaid Medical Insurance. The Committee had been continuing its studies and will be ready to make a further and more specific report during the Annual Session of the College in April.

Dr. George F. Strong, Chairman, reported for the Coöperative Committee with the Royal Colleges, the purpose being to develop a coöperative exchange relationship among the Royal Australasian College of Physicians, the Royal College of Physicians of London, The American College of Physicians, and others. The Committee recommended that the American College of Physicians propose to the Royal Australasian College of Physicians that, in order to further the friendly relations between our two Colleges, the following arrangement be entered into:

> "That when the Royal Australasian College of Physicians desires to invite one of our Fellows to visit one of their annual meetings or the Schools of Medicine of the Australasian Universities, or to contribute in any other way to postgraduate instruction, the American College of Physicians will furnish one-half the funds required for the travel expenses involved. Reciprocally when a Fellow of the Royal Australasian College is invited to participate in medical activities of the American College of Physicians, a similar sharing of the travel expenses would take effect."

It was suggested that Dr. Richard A. Kern, Secretary General of the American College of Physicians, in connection with his proposed trip to Australia and New Zealand, during 1955, discuss the above matter with the Dominion Committee of the Royal Australasian College of Physicians, with the authority and approval of the Board of Regents. In regard to the Royal College of Physicians of London, the Committee recommended that informal discussion be continued.

Dr. Walter L. Palmer, Chairman, reported for the Editorial Board of the ANNALS OF INTERNAL MEDICINE. He indicated the approval of the Board of the operation of the Journal and expressed complete satisfaction. Recommendations were presented for advancement in the salary of the Editor and Assistant Editor; for an increase in the advertising rate, because of the fast expanding circulation, on January 1, 1956, approximately 20%; beginning as soon as practicable, the Editor shall be authorized to add at the end of each scientific article a summary published in Interlingua; for the News Notes Section of the Journal to be paged separately from the scientific section (probably by Roman numerals). All recommendations were formally approved by the Regents through appropriate resolutions.

Dr. Edward L. Bortz, Chairman, presented the report of the Committee on Educational Policy, his report dealing with certain communications having to do with relative duties and standing of the internist in hospital organization; the March of Medicine telecast program; the analysis of the 1954 Annual Session program at Chicago, with regard to approval or disapproval by the members, etc. The Committee formally recommended certain features and schedules for the Philadelphia Session, including correlation between Panel Discussions and Clinical-Pathological Conferences, and further opportunities for discussion at Clinical-Pathological Conferences by the attendants. Dr. Bortz then reviewed the evaluation of the experimental television broadcast by the College in September, 1954, with the conclusion that that program was of high quality of performance, exceedingly well done, and had proved a great stimulus to a new type of promoting postgraduate medical educa-

tion. Dr. Bortz proposed that a special committee be appointed to study further this type of teaching and to function in case of the further extension of the program by the College. The report of the Committee was approved, and the President was requested to appoint a special committee. (The President later ruled that no special committee was indicated, and that these duties should properly fall upon the present Committee on Educational Policy.)

Dr. Wallace M. Yater, Chairman, reported on the work of the Committee on Medical Educational Films, stating that two films were in preparation, namely, "Pitfalls in Cardiovascular Therapy" and "Treatment of Pre-Menstrual Tension." The Committee suggested that the present Committee on Educational Policy consider the possibility of making a sound motion picture film of some of the fine panels on the Annual Session program of the College, following out the same idea as the television program, but being much less expensive, and yet of great educational value, because the films could be duplicated and made available at a small fee to various medical schools, hospitals, county societies and others throughout the land.

Dr. Yater then proceeded to report for the Portrait Committee, which has been disbanded. He turned over to the College, $677.59 for the purpose of preserving properly all portraits, photographs, drawings, and other likenesses of members of the College and/or its staff. This balance had remained after the completion of the portrait of the Executive Secretary, Mr. E. R. Loveland.

Dr. William D. Stroud, Chairman, presented a report for the House Committee, dealing primarily with the disposition of the property belonging to and adjoining the College. The Board of Regents adopted a resolution giving authority to the House Committee to dispose of this property, or to alter it for such use as the Committee might desire, subject to the final approval of the Executive Committee. The President and several others, including members of the House Committee, suggested the desirability of razing the house and retaining the ground for future purposes of the College and currently as a parking area for College staff members and Fellows.

Dr. Walter L. Palmer, Chairman of a special committee appointed by the President to study the matter of fees and dues and certain other items presented the following recommendations which were approved by the Regents:

(1) The College shall establish a Revolving Loan Fund, for the assistance of residents in medicine in accredited hospitals; $20,000.00 per year to be set aside for five years; the President and Finance Committee to present at the next meeting proposed regulations for its operation; no interest to be charged for such loans until three years after the completion of the residency, and from that time forward 3% per annum, the loan to be repaid at any time within ten years from date of issue. The suggestion was made that applications for loans should bear the endorsement of the College Governor for the area from which the applicant comes;

(2) That the President be authorized to negotiate with the Kellogg Foundation, or other foundations, with the hope that they will match the funds set aside by the College for the Revolving Loan Fund.

(3) Annual Dues: The Committee, although congratulating the College, its Officers, Regents and Executive Secretary on the achievement of maintaining the dues at the same level for the past twenty-five or more years, believes, in view of the fact that the dues are low in comparison with those of other organizations, and because the activities and financial commitments are numerous and constantly increasing, the dues should be increased as follows on January 1, 1955: Masters and Fellows, in actual practice, from $20.00 to $25.00 per year; Associates in practice, from $15.00 to $18.00 per year; whole-time teachers, research workers and military personnel—continue at $12.00 per year; Life Membership—increased commensurately, according to formula, with above changes.

Dr. Cyrus C. Sturgis, President, and Dr. Thomas M. Durant, General Chairman, reviewed in considerable detail the plans and program for the 1955 Annual Session at Philadelphia.

A resolution was adopted, directing the Executive Secretary to make a nominal charge of $2.00 per ticket for the Symphony Concert, scheduled for the first evening of the Convention.

A resolution was adopted, directing the President, Secretary-General, General Chairman and Executive Secretary to attempt to work out a more convenient and effective schedule for meetings of the Board of Regents and Board of Governors at the Annual Session, and to prepare, likewise, a more convenient schedule of Committee meetings and the Regents' meeting in the autumn. A specific resolution was adopted, directing that at the next mid-autumn meeting of the Board of Regents, Committee meetings shall start on Friday, the Board of Regents meeting on Saturday afternoon, to be continued on Sunday, if need be, thus releasing members of the Board of Regents by noon on Sunday.

A resolution was adopted, giving authority to the Chairman of the Committee on Credentials and to the Executive Secretary to augment the Committee on Credentials by two experienced men when pressure of work demands.

Adjournment.

OBITUARIES

DR. ELLERY G. ALLEN

Dr. Ellery George Allen, F.A.C.P., of Syracuse, N. Y., died on Jan. 4, 1955, from rheumatic heart disease.

Dr. Allen was graduated from Colgate University with a B.S. degree in 1922 and from Harvard Medical School in 1926. He served as an intern at the Methodist Hospital in Brooklyn from 1926–28 and as resident at the University Hospital from 1928–29.

He was identified with Syracuse University College of Medicine as Instructor in Medicine, then Associate and Clinical Professor of Medicine and also as Associate Professor of Clinical Pathology, and later as Clinical Professor of Medicine at the State University of New York College of Medicine, Syracuse. He was a Diplomate of the American Board of Internal Medicine. His major interest was in hematology.

Dr. Allen was Attending Physician and Attending Hematologist at St. Joseph's Hospital, Consultant at Syracuse Memorial Hospital and at the Oneida City Hospital.

Dr. Allen was elected a Fellow of the American College of Physicians in 1939 and was always very active in the Western New York Regional Meetings of the College. He was also a member of the Syracuse Academy of Medicine, Onondaga County Medical Society, Medical Society of the State of New York, American Medical Association, and the American Federation of Clinical Research. While at Colgate he was a member of Lambda Chi Alpha Fraternity and at Harvard was a member of Phi Beta Pi Medical Society.

Dr. Allen was a very well-trained internist with especial attention directed to hematology. He was scholarly, an ardent student, industrious, honest, and humane. His opinion was highly respected by his colleagues. He will be greatly mourned by many of his friends and colleagues.

Dr. Allen was associated with me for three years in my office. I always found him very conscientious, studious, industrious, ethical and honest. He was a man of high standards, humane, lovable and well-liked by all of his friends. I have suffered a personal loss in the death of Dr. Allen.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. J. REID BRODERICK

John Reid Broderick, Sr., M.D., F.A.C.P., died in Savannah, Ga., where he was born Oct. 3, 1898, at the St. Joseph's Hospital at 7:05 P.M., Nov. 7, 1954.

He graduated from the Savannah High School, attended Georgetown University and received his medical training at Jefferson Medical College of Philadelphia, graduating in 1925. He served his internship at St. Vincent's Hospital in Erie, Pa., and served as resident physician in Savannah at the Telfair Hospital and later at the Central of Georgia Railway Hospital.

Dr. Broderick, affectionately known as Reid, entered the private practice of internal medicine, July 1, 1928, and was immediately successful, earning very quickly the confidence and respect of his patients, his fellow physicians, and the general public. Because of his unusual devotion to his patients and because of his lovable disposition, his practice grew to such proportions that he had little time for himself and family.

Many honors came to him in the course of his practice of medicine. He served on the staffs of most of the hospitals in Savannah as Consultant in Internal Medicine and Cardiology. He was a past President of the St. Joseph's Hospital Staff and at the time of his death he was Chairman of its Board of Governors. He was a member

and past President of the Georgia Medical Society, a member of the Medical Association of Georgia, the Southern Medical Association and the American Medical Association. He had been a Fellow of the American College of Physicians since 1931.

Dr. Broderick was equally diligent in the performance of his civic and religious duties. He was a member of the Rotary, Oglethorpe, Savannah Yacht and Country Clubs. He was a member and Vice President of the Hibernian Society and had served on the Board of Education and the Board of Sanitary Commissioners of Chatham County.

A devout member of the Catholic Church, he took an active interest in the affairs of the church. He was past President of the Catholic Laymen's Association of Georgia and Permanent Chairman of the Bishop's Confraternity of the Laity for the Savannah and Atlanta Diocese. He was a member of the Fourth Degree Assembly of the Knights of Columbus and of the Holy Name Society of the Sacred Heart Church, of which he was a communicant.

The confidence inspired by this truly great physician in the hearts of all those with whom he came in contact soon grew into a deep and abiding affection. He gave of himself generously to those who were ill, rich and poor alike, and to his fellow physicians, literally wearing himself out in the service of others. He will be greatly missed by those who were privileged to know him.

JOHN L. ELLIOTT, M.D. (Associate)
CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. JAMES G. CARR

Dr. James Gray Carr, F.A.C.P., 78, Emeritus Professor of Medicine of Northwestern University Medical School and former Chief of the Medical Staff of Evanston Hospital, died Oct. 17, 1954, of cerebral arteriosclerosis.

Dr. Carr was born at Holmesville, Ohio, July 22, 1876, and received his A.B. degree from Ohio State University in 1897. He attended Northwestern University Medical School and received his M.D. degree in 1902. For many years Dr. Carr was Secretary of the Northwestern Medical Faculty.

He was a devoted, loyal, and hard working member of the American College of Physicians, being a Fellow of the College since 1926. Dr. Carr served as Governor for Northern Illinois from 1929–40, and was Second Vice President from 1940–41. He was also active on many important College Committees.

Dr. Carr served on the staffs of Passavant, Wesley Memorial, Mercy, South Shore, and Cook County Hospitals. He was an able practitioner of Internal Medicine and a sincere, stimulating teacher. His medical service at Cook County Hospital was always very attractive to the house staff.

He was one of the founders and past Presidents of the Chicago Heart Association. At Northwestern University Medical School, he was the Director of the Florsheim Foundation for the study of heart disease. He was a member of, and active in, many medical organizations, including the Chicago Medical Society, Illinois State Medical Society, American Medical Association, Chicago Pathological Society, Central Society for Clinical Research, Chicago Society of Internal Medicine, the Institute of Medicine of Chicago, and the American Heart Association. He was a Diplomate of the American Board of Internal Medicine, and in 1939 received the Distinguished Service Award of the Mississippi Valley Medical Association.

It is with regret that his confreres record his passing.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. D. J. DAVIS

Dr. David John Davis, F.A.C.P., died Dec. 19, 1954, at his home in Wilmette, Ill. Dr. Davis was born Aug. 9, 1875, in Racine, Wis. He did his undergraduate work at the University of Wisconsin and received his B.S. degree there in 1898. He went on to Rush Medical College and received his M.D. degree in 1904.

Dr. Davis was always an outstanding student with an inquiring mind, and it was natural for him to continue with his graduate work at the University of Chicago, where he received his Ph.D. degree in pathology under the guidance and inspiration of one of the giants of American pathology, the late Ludvig Hektoen.

He continued his graduate studies in bacteriology and pathology in Vienna and Freiburg. He joined the Department of Pathology at the University of Illinois in 1913 and served that Department as Professor and Chairman for thirty years until his retirement in 1943. In addition, he was Dean of the College of Medicine at Illinois from 1925 until 1943.

He was the author of about one hundred and twenty-five papers dealing chiefly with infectious disease. He was a leader in medical education during the period when the medical schools of the United States were undergoing many changes for the better. His thinking and actions were always on the frontier, both in his investigative work on infectious diseases and in the techniques of medical education.

At one time Dr. Davis was President of the Board of Directors of the Chicago Municipal Tuberculosis Sanatorium, also President of the Institute of Medicine of Chicago. He had a great interest in medical history, so it was natural for him to have been the permanent Historian of the Illinois State Medical Society since 1945. He was the Editor of Volume II of *History of the Practice of Medicine in Illinois.*

He loved Welsh music and frequently he would sing Welsh songs very lustily in the presence of his friends, who in turn would join him in the singing with just as much gusto.

Dr. Davis was a former President of the Chicago Pathological Society, a member of the Chicago Medical Society, Illinois State Medical Society, American Medical Association, Chicago Society of Internal Medicine, American Association of Pathologists and Bacteriologists, Society of American Bacteriologists, and the American Association of the History of Medicine. Dr. Davis became a Fellow of the American College of Physicians in 1922. He was a member of three honorary fraternities—Sigma Xi, Phi Beta Kappa, and Alpha Omega Alpha.

American Medicine, and particularly medicine in the Middle West, has lost an outstanding leader in pathology and bacteriology, a distinguished investigator in his chosen fields, a leader in medical education, in the death of Dr. Davis. He was a gentleman and a real scholar. He leaves a host of friends and admirers, his wife Myra and two children.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. E. A. DELARUE, JR.

Edward Arthur Delarue, Jr., M.D., F.A.C.P., of Richmond, Va., died Sept. 19, 1954, of coronary thrombosis. A native of Richmond, Dr. Delarue was graduated from the University of Virginia in 1929 with a B.S. degree and received his M.D. from the University of Virginia Department of Medicine in 1933. After an internship at the Peter Bent Brigham Hospital, Boston, Dr. Delarue served his residency at Kings County Hospital, Brooklyn, N. Y., and at Willard Parker Hospital, New York City.

Dr. Delarue returned to Richmond in 1937 when he joined the faculty of the Medical College of Virginia as an Assistant in Medicine. He later became an In-

structor and at the time of his death held the rank of Associate in Medicine. He was also Assistant Physician in the College's Hospital Division, Attending Physician to the Veterans Administration Hospital, and to the Sheltering Arms Hospital, where he had once been Chief of Medicine. During World War II, Dr. Delarue served as Major, (MC), AUS from May, 1942, until May, 1946.

A member of the Richmond Academy of Medicine, Dr. Delarue also held memberships in the Medical Society of Virginia, American Medical Association, and Phi Beta Kappa and Alpha Omega Alpha fraternities. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1943.

He was faithful in attendance at all worthwhile medical scientific gatherings since beginning practice in Richmond. In addition he contributed much time and effort in the Cardiac Clinic at the Medical College of Virginia.

Dr. Delarue never married but resided with his parents in Richmond, where he was born in 1907. He had never been ill but suffered an acute attack of coronary thrombosis while tending a patient in a local hospital and he survived only a few days. He will be missed keenly by his professional colleagues, his family and his friends.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

DR. HOMER DONALD

Dr. Homer Donald, F.A.C.P., of Dallas, Tex., died at his home Oct. 20, 1954, of a myocardial infarction.

Dr. Donald was born in Lewisville, Tex., Nov. 14, 1886. He received his premedical education at Trinity University, Waxahachie, Tex, and Westminster College, New Wilmington, Pa. He graduated from the University of Texas School of Medicine in 1912 and served an internship at the John Sealy Hospital in Galveston, 1912–13. He began the practice of internal medicine in Dallas in 1913. He was an Instructor in Clinical Medicine at the Medical School of Southwestern University, 1914–16. In 1916 he became an Associate in Medicine in Baylor University College of Medicine, and successively was Assistant Professor and Associate Professor of Clinical Medicine, serving continuously on the faculty of that institution until 1942. From 1951–54 he was Consultant in Medicine at the Southwestern Medical School of the University of Texas. Dr. Donald had been a member of the staff of Baylor University Hospital and Methodist Hospital for many years.

He served as President of the Dallas County Medical Society in 1941. He was active in organized medicine throughout his professional career and had been a member continuously of the Dallas County Medical Society, North Texas, Texas, Southern and American Medical Associations. He was formerly a member of the American Congress on Internal Medicine and became a Fellow of the American College of Physicians in 1922. Dr. Donald was a founder of the Dallas County Medical Plan, an organization providing medical and surgical care for employed low-income groups.

He was a man of broad civic interests and was recognized as a leader in his church and in many community activities. A quiet, reserved, friendly man, a competent physician and teacher of medicine, Dr. Donald was held in high esteem by his colleagues and his patients. The profession of Dallas and Texas has suffered a great loss in his passing.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. EDWIN G. FABER

Dr. Edwin Gabriel Faber, F.A.C.P., died in Tyler, Tex., Dec. 8, 1954, of a coronary thrombosis.

Dr. Faber was born in Titusville, Pa., June 26, 1896. He attended the universities of Texas and Colorado and received his M.D. degree from the University of Colorado School of Medicine in 1919. He served an internship at St Luke's Hospital, 1919–20, and was resident physician at Children's Hospital in Denver, 1920–21. He was an Instructor in Medicine in the University of Colorado School of Medicine, 1925–35, and was Director of the Outpatient Department, 1926–28. He was a member of the Attending Staff of St. Luke's and Mercy Hospitals, 1925–35. At the time of his death, Dr. Faber was a member of the Attending Staff of the Mother Frances Hospital of Tyler. He had been President of the Executive Staff in 1942 and Chief of the Department of Medicine in 1946. He had served this institution continuously since 1937 with the exception of the years 1942–46 when he was in the Army of the United States. He was separated from the service as a Colonel.

Dr. Faber was Clinical Assistant Professor of Medicine at Southwestern Medical School of the University of Texas from 1946–53, when he resigned because of ill health.

Dr. Faber was a Diplomate of the American Board of Internal Medicine. He had served as President of the Texas Tuberculosis Association, 1940–42. He was a member of the National Tuberculosis Association, Southern Medical and American Medical Associations and of the American Trudeau Society. He was a Fellow of the American College of Allergy and became a Fellow of the American College of Physicians in 1942.

As a pioneer internist in his community, Dr. Faber did much to advance the practice of medicine there.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. ERNEST E. HADLEY

Dr. Ernest Elvin Hadley, F.A.C.P., nationally known psychoanalyst of Washington, D. C., died unexpectedly on Aug. 10, 1954, following an operation.

Born in Alton, Kans., Aug. 2, 1894, he received the degree of Bachelor of Science in Medicine from the University of Kansas in 1918 and his medical degree from the same institution in 1920. He was the first civilian intern at the Walter Reed Army Hospital, Washington, D. C., 1920–21. He than became a member of the psychiatric staff of Saint Elizabeths Hospital in Washington until 1929, when he resigned to enter the private practice of psychoanalysis.

At the time of his death, Dr. Hadley was President of the Washington Psychoanalytic Society and Director of the Washington Psychoanalytic Institute. He had been Consultant to the Veterans Administration, conducting weekly seminars in the local Mental Hygiene Clinic; Consultant to the Corporate Foundation for Research and Training in Psychiatry, Teacher at the New Orleans Psychoanalytic Training Center, and Fellow of the Board on Professional Standards of the American Psychoanalytic Association. For many years he contributed reviews and articles to scientific publications.

Dr. Hadley organized, and from 1933 to 1945 he was Trustee and Secretary of, the William Alanson White Psychiatric Foundation. He founded the journal *Psychiatry* and was Co-editor from 1938 to 1945. Active in the affairs of the Washington School of Psychiatry, Dr. Hadley was Secretary (1936–45), Director (1936–43), Director Emeritus (1943), and Fellow (1943–45). He served as Chairman of the Central Examining Board for Neurology and Psychiatry, Selective Service System, in 1941, and was also Chairman of the Psychiatry Panel, Army Induction Board, Fort Myer, Va., from 1942 to 1944.

A four-term President of the Washington Psychoanalytic Society, Dr. Hadley had also served as President of the Washington Society for Mental and Nervous Diseases, Washington Psychopathological Society, and of the George M. Kober Medical Society, of which he was a charter member. He was also a former Secretary of the American Psychoanalytic Association and a member of the Washington Psychiatric Society, Southern Psychiatric Association, Medical Society of the District of Columbia, Tri-State Medical Association, American Medical Association, Association of American Physicians, World Federation for Mental Health, American Eugenics Society, New York Academy of Science, and Phi Beta Pi fraternity. He was elected a Fellow of the American College of Physicians in 1938.

There are many here who are deeply indebted to him for his encouragement, his gentle kindness and understanding, his advice and wisdom. The past 25 years he devoted much time and energy to the training of physicians in psychoanalysis. His last duty, after a full day at the office from 6:30 in the morning, was the interview of a prospective student, held on the evening of Aug. 3. He will now live on in the work of his students and all those who came in contact with him.

JOHN MINOR, M.D., F.A.C.P.,
Governor for the District of Columbia

DR. PAUL M. HOLMES

The Fellowship of the American College of Physicians throughout Ohio, and more particularly in Toledo, were saddened by the death of Dr. Paul McKinley Holmes, F.A.C.P., on Aug. 17, 1954, aged 64 years.

Born in Columbus, Ohio, at the beginning of the last decade before the turn of the century, Paul Holmes graduated from the first class in the newly established College of Medicine on the Ohio State University campus in 1914. During War I, he was on active duty with the United States Public Health Service, with the rank of Assistant Surgeon, conducting health hazard surveys in 1918–19. He later became Physician-in-Charge of the Lucas County Tuberculosis Hospital and Dispensary from 1922 to 1938 and was a member of the Dispensary Staff at St. Vincent's Hospital. He was Medical Director of the Oak Ridge Sanatorium, Green Springs, from 1933 to 1954. He was an active member of the Attending Staff of the Toledo State Hospital since 1925 and of the Toledo Hospital since 1929. He had been a Consultant in Tuberculosis to the Robinwood Hospital since 1934 and an Attending Physician to the Toledo Society for Crippled Children Convalescent Home since 1939. Formerly he was Medical Director of the William W. Roche Memorial Hospital, and former Chest Examiner for the U. S. Veterans Administration. He was a member of the Board of Consultants for Occupational Diseases of the Industrial Commission of Ohio.

He was honored with the Presidency of the Academy of Medicine of Toledo and Lucas County in 1945. Dr. Holmes maintained membership in the Ohio State and American Medical Associations, the National Tuberculosis Association, the Ohio Hospital Superintendents Association, the American College of Chest Physicians, and the Academy of Tuberculosis Physicians.

He was a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians for 26 years.

Dr. Holmes endeared himself to everyone who knew him, both professionally and personally. He was a leader in his community and in the fields of medicine which embraced his interests and commanded his time and thought. The sincere sympathy and condolences of the entire membership of the College in Ohio are extended to his family and to his friends.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. WILLIAM E. JONES, SR.

Dr. William Edgar Jones, Sr. (Associate), of Texarkana, Tex., died there on July 3, 1954.

Dr. Jones was born in Dallas, Tex., on Sept. 26, 1914. He attended Southern Methodist University and was graduated from the University of Texas School of Medicine in 1938. He served an internship and was a resident physician at the Henry Ford Hospital in Detroit, Mich., from 1938 to 1941. From 1941 to 1946 Dr. Jones was on active duty in the Medical Corps of the Army of the United States. He served in the China-Burma-India theater with the 95th Station Hospital for a period of eighteen months. He was a student of tropical medicine at the Calcutta (India) School of Tropical Medicine in 1942 and did postgraduate work in gastroenterology at the Mayo Clinic in January and February of that year. He was discharged from the military service in February, 1946, as a Lieutenant Colonel.

He practiced in Dallas for a short period of time, but in 1947 he moved to Texarkana, Tex. He was a member of the Texas and American Medical Associations and was certified by the American Board of Internal Medicine. He was also a member of the Southern Medical, Texas Heart and the American Heart Associations. He was a Fellow of the National Gastroenterological Association, the American Geriatrics Society, and the International Academy of Medicine. He was elected to Associateship in the American College of Physicians in 1952. He was on the staffs of St. Michael's and Texarkana Hospitals in Texarkana.

Dr. Jones was a member of Alpha Omega Alpha and Phi Chi fraternities. He lectured on tropical medicine in the University of Arkansas School of Medicine and had held the rank of Associate Professor of Medicine in that institution for several years.

Dr. Jones' early death terminated a promising career.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. ERNEST ELLSWORTH KEET, SR.

Dr. Ernest Ellsworth Keet, Sr., a Fellow of the American College of Physicians, died on Oct. 5, 1954, of what was diagnosed as myocardial infarction.

He was born in Schuyler Falls, N. Y., on Feb. 23, 1884. He received the degree of Doctor of Medicine from Cornell University Medical College in 1907 and took postgraduate work in medicine, surgery, obstetrics, and gynecology at the Lincoln Hospital from 1908–10. He was associated with the late Dr. James Alexander Miller, M.A.C.P., on the Tuberculosis Service of the Bellevue Hospital from 1910–12. Dr. Keet was the former Attending Physician and President of the Staff (1926–28) of the Queensboro Hospital, former Attending in Medicine, Medical Director and President of the Staff of Jamaica Hospital. He was a member of the Associated Physicians of Long Island, the Queens County Medical Society, Medical Society of the State of New York, and the American Medical Association. He became a Fellow of the American College of Physicians in 1930.

Dr. Keet's friends and confreres note his passing with deep regret.

Irving S. Wright, M.D., F.A.C.P.,
Governor for Eastern New York

DR. HARRY C. KROON

Dr. Harry Charles Kroon, F.A.C.P., of Syracuse, N. Y., died on Nov. 15, 1954, from an acute attack of coronary occlusion.

Dr. Kroon was born in New York City in 1905 and graduated from Syracuse University College of Medicine in 1932. He served as intern at the Hospital of the

Good Shepherd from 1932–33 and as resident at the same hospital from 1933–34. He was Associate Attending Physician at the Hospital of the Good Shepherd, City Hospital, and Syracuse Free Dispensary; and Attending Physician for Cardiology at the Veterans Administration Regional Diagnostic Clinic at Syracuse. Dr. Kroon was Assistant Professor of Medicine at the Syracuse University College of Medicine and at the State University of New York College of Medicine at Syracuse. He was a member of the Association of Military Surgeons of the United States and served as Major and Lieutenant Colonel in the Medical Corps of the Army Air Force from 1942–45.

Dr. Kroon was a member of the Syracuse Academy of Medicine, Onondaga County Medical Society, American Heart Association, American Medical Association and a Diplomate of the American Board of Internal Medicine. He had been a Fellow of the American College of Physicians since 1944.

Dr. Kroon was a very highly respected physician in Syracuse. His death will be deeply felt by his friends, patients and professional colleagues.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. FRANK WILLIAM MACKOY

Dr. Frank William Mackoy (Associate), died on Aug. 17, 1954, of arteriosclerotic heart disease.

Dr. Mackoy was born in 1879 at Siloam, Ky., and received his M.D. degree from the University of Illinois College of Medicine in 1905. While serving in the Armed Forces during World War I, he became interested in roentgenology and did postgraduate work in that field at Cook County Hospital in Chicago in 1919 and at the University of Michigan in 1920. From 1927 he served as Roentgenologist at the Sacred Heart and St. Mary's Hill Sanitaria in Milwaukee but continued his interest in clinical internal medicine during that entire period. In 1936 he was named Clinical Professor and Director of the Division of Roentgenology at Marquette University School of Medicine, in which capacity he served with distinction until his resignation in 1941.

He was a Diplomate of the American Board of Radiology, a Fellow of the American College of Radiology, member of the American Medical Association, National Gastroenterological Association, Radiological Society of North America, Milwaukee Academy of Medicine, Milwaukee Roentgen Ray Society and the Milwaukee Gastroenterological Society, of which he was President in 1938. He had been an Associate of the American College of Physicians, through the American Congress on Internal Medicine, since 1922.

Dr. Mackoy was a pioneer in several aspects of diagnostic roentgenology, especially those having to do with the gastro-intestinal tract, and contributed much to the development of that field. Because of his continued interest in the field of internal medicine, he also contributed greatly to the correlation of roentgenology with clinical medicine. He was highly esteemed and respected by his colleagues and by all of those with whom he had personal contact.

FREDERICK W. MADISON, M.D., F.A.C.P.,
Governor for Wisconsin

DR. ROBERT S. McCAUGHEY

Dr. Robert Stanton McCaughey, F.A.C.P., was born in Hoopeston, Ill., Sept. 16, 1875, and died on Aug. 9, 1954, at Danville, Ill., of pulmonary embolism following a fractured hip.

After receiving his A.B. degree from Monmouth College in 1899 and his M.D. degree from Rush Medical College in 1902, he continued with postgraduate studies

at his alma mater and at the University of Berlin. He became an Assistant and later an Associate in Medicine at Rush. In 1915 Dr. McCaughey began the practice of medicine in Danville. From 1917 to 1919 he served in the Medical Corps of the Army, with the rank of Major, first at Camp Sherman, Ohio, and later as Chief of the Medical Service in Base Hospital No. 112, A.E.F. After World War I, he returned to Danville, where he became an Attending Physician at Lake View Hospital until his death and Director of the Vermilion County Tuberculosis Dispensary and Hospital until 1940.

In addition to his membership in the local and state medical societies (of which he was a fifty-year member), Dr. McCaughey was a member of the American Medical Association and the National Tuberculosis Association. He became a Fellow of the American College of Physicians in 1925 and was a Diplomate of the American Board of Internal Medicine.

Dr. McCaughey was highly respected by his colleagues for his integrity, ability, and the courage of his convictions. His loss will be felt deeply by his associates, patients, and many friends.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. VIRGIL F. NEUMANN

Dr. Virgil Frank Neumann, F.A.C.P., was born in Bay City, Mich., Jan. 4, 1902. He was graduated from the University of Michigan Medical School in 1929. He had a one-year internship at Henry Ford Hospital in Detroit, and following this, spent about a year at Herman Kiefer Hospital, Detroit, in contagious disease work. He then became resident physician at the Uncas-on-Thames State Tuberculosis Sanatorium at Norwich, Conn., and remained as a member of the staff of this hospital for the following eighteen years. He was then appointed to the staff of State Tuberculosis Hospital No. 2 at Cresson, Pa.

From August, 1953, until Aug. 30, 1954, Dr. Neumann was Senior Staff Physician at the Saginaw County (Mich.) Tuberculosis Hospital. At this time he was appointed Medical Director of the American Legion Hospital at Battle Creek, Mich., and assumed this post Aug. 31, 1954. He died suddenly Sept. 1, 1954, at 52 years of age.

Dr. Neumann had been a Fellow of the American College of Physicians since 1944 and also held memberships in the American College of Chest Physicians, American Diabetes Association, and the American Trudeau Society. His chief interests were tuberculosis and, particularly, diabetes.

H. M. POLLARD, M.D., F.A.C.P.,
Governor for Michigan

DR. C. H. PAINE, SR.

Charles Herman Paine, Sr., M.D. (Associate), Atlanta, Ga., was born in Valdosta, Ga., April 20, 1887. He died of a myocardial infarction on Sept. 4, 1954.

Dr. Paine attended Potter Bible College, Bowling Green, Ky., where he received his B.S. degree in 1907. He then attended the Atlanta College of Physicians and Surgeons, receiving his M.D. degree in 1911. He interned at Piedmont Hospital in Atlanta from 1911 to 1913. He then did postgraduate work in New York City at the Lying-In Hospital, Polyclinic Hospital, Outdoor Dispensaries, St. Mary's and Mt. Sinai Hospitals in 1913.

In 1914, Dr. Paine returned to Atlanta and entered private practice, where he was associated with the late Dr. C. W. Strickler, Sr., F.A.C.P., for many years. He served as Clinical Instructor, Associate in Medicine, and Assistant Professor of Medicine on the faculty of Emory University School of Medicine. He was a mem-

ber of the staff of Emory University Hospital, Grady Memorial Hospital, and Georgia Baptist Hospital.

Dr. Paine was made an Associate in the American College of Physicians in 1920 through the American Congress on Internal Medicine. He was also a member of the Medical Association of Georgia, the Southern Medical Association, and the American Medical Association.

He was a member of the Church of Christ in Atlanta and held the office of Elder for many years. He also was a member of the Phi Chi Medical Fraternity.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. ANDREW B. STOCKTON

It is with regret that we announce the death of Dr. Andrew Benton Stockton, F.A.C.P., on Sept. 6, 1954.

Dr. Stockton was born in Spokane, Wash., on Jan. 18, 1900. His graduate education first occurred at the U. S. Naval Academy, where he was enrolled for one and a half years, before transferring to Stanford University, where he received his A.B. degree in 1923. In 1928 he obtained his M.D. degree at Stanford University School of Medicine and served an internship and assistant residency in medicine at the Stanford University Hospitals.

At Stanford University School of Medicine, Dr. Stockton was, successively, Assistant Instructor in Pharmacology, Instructor in Therapeutics, Assistant Professor of Therapeutics, and at the time of his death, Assistant Clinical Professor of Medicine, which position he had held since 1938. He was Chief of Medicine at the San Francisco Polyclinic since 1947 and a member of the Visiting Staffs of the French, Notre Dame, St. Mary's, and Mary's Help Hospitals. During World War II he served as Lieutenant Commander, (MC), USNR. He was a member of the San Francisco County Medical Society, California and American Medical Associations, California Academy of Medicine, Society for Experimental Biology and Medicine, American Association for the Advancement of Science and Sigma Xi fraternity. He had been a Fellow of the American College of Physicians since 1944.

Dr. Stockton was well liked by his associates in San Francisco and was held in high esteem as a clinician and physician.

STACY R. METTIER, M.D., F.A.C.P.,
Governor for Northern California and Nevada

DR. MAX S. WRIGHT

Dr. Max Singer Wright, F.A.C.P., Spokane, Wash., died of a heart attack on Dec. 8, 1954.

Dr. Wright was born in Grand Rapids, Mich., on March 25, 1903, and attended the University of Michigan, where he received his B.S. (Med.) degree in 1925 and in 1927 was graduated from the University of Michigan Medical School. After an internship at Swedish Hospital, Seattle, in 1927–28, Dr. Wright practiced general medicine at Sedro-Woolley, Wash., until 1930. For the following five years he was Assistant Health Officer for the City of Spokane and also served as Assistant County Physician, Spokane County, from 1935–39. From 1939–41 Dr. Wright was Medical Superintendent of the Spokane County Hospital in Spangle before he resumed private practice in 1941. He was a member of the Spokane County Medical Society, the Washington State and American Medical Associations; he became a Fellow of the American College of Physicians in 1941.

Dr. Wright's principal medical interest lay in the field of geriatrics. He will be missed by many devoted patients in that group.

GEORGE H. ANDERSON, M.D., F.A.C.P.
Governor for Washington